PROCEEDINGS
OF THE
ROYAL SOCIETY OF MEDICINE

Vol. 49 No. 1 January 1956

CONTENTS

Continued overleaf

CONTENTS (*continued*)

N.B.—The Society does not hold itself in any way responsible for the statements made or the views put forward in the various papers.

Proceedings of the Royal Society of Medicine Vol. 49 1

Section of Urology

President—DAVID BAND, F.R.C.S.Ed.

[*October* 27, 1955]

The Management of Genito-urinary Tuberculosis in the Special Hospital

PRESIDENT'S ADDRESS

By DAVID BAND, F.R.C.S.Ed.

Reader in Urological Surgery, University of Edinburgh

(*From the Department of Surgery, University of Edinburgh*)

WITH 92 empty beds in East Fortune Hospital at Edinburgh, I am presenting a series of cases of genito-urinary tuberculosis which have been observed, treated and followed during the past five years, and which I believe may be the last regional series of statistical significance.

In any survey of focal tuberculosis, it is necessary to recall that the four stages in the evolution of the disease are: (1) the period of incubation, (2) the period of invasion, (3) the period of visceral spread and (4) the period of advanced caseo-cavernous pulmonary tuberculosis.

In the management of genito-urinary tuberculosis, tubercle bacilluria must be regarded as evidence that the second invasive stage of tuberculosis has been successful and that the third stage of visceral spread has begun. Nevertheless, adequate measures taken to build up the patient's resistance, and antibiotic or other therapy directed towards such tuberculous lesions as are demonstrable, may lead to permanent cessation of tubercle bacilluria and to the return of the patient to health and strength. Frank renal tuberculosis following tubercle bacilluria occurs in a very low percentage of patients. Therapeutic measures for the treatment of bacilluria should be as intensive and prolonged as for the treatment of any other clinically recognizable focus of tuberculous infection.

In an earlier series (1935–1945) of 50 cases of genito-urinary tuberculosis in the male, 20% suffered from a lesion which clinically was limited to the genital tract, and few, if any, of those cases would have been recognized had there been no involvement of the epididymis. In order of frequency, clinical genital tuberculosis was recognized (1) in the epididymis (100% of cases), (2) in the seminal vesicles (75%) and (3) in the prostate (17·8%). However, these figures were at variance with those reported elsewhere. Moore (1937) made an autopsy study of the genital tract in 20 cases of tuberculous prostatitis and found vesicular lesions in only 15%. He believed that in tuberculous disease of the prostate the lesions were blood-borne because they were distributed in the peripheral zones of the prostate, whereas a urethral spread by contiguity produced lesions close to the lumen of the prostatic urethra. In an autopsy study of 62 cases of genital tuberculosis, Menville and Priestley (1938) found renal and prostatic tuberculosis closely associated. At the same time they noted that the epididymis was frequently involved whereas the prostate remained normal. Hammond (1941) stressed the difficulties in attempting to assess the pathogenesis and mode of spread in genital tuberculosis. However, it should not be forgotten that the testis and epididymis have a generous blood supply through the spermatic artery and the artery to the vas deferens, the one from the aorta and the other from the internal iliac through its inferior vesical branch. Similarly the prostate, seminal vesicles and ampulla of the vas deferens are all supplied by the inferior vesical and middle rectal branches of the internal iliac artery. The close relationship of these structures to one another in the median line in front of the rectum, and the intercommunications in the lymphatic drainage as well as the intraluminal connexions through the ducts, provide alternative routes for the spread of infection in the genital tract once a tuberculous focus has become established and activated. Thus tuberculosis may (1) occur in the prostate as a peripheral lesion, (2) ascend from the posterior urethra via the ejaculatory duct to the vesicles and prostate, or by way of the vas to the epididymis, (3) descend from

the epididymis via the vas to the vesicles and prostate and by the ejaculatory ducts to the urethra.

Coincidence of renal and genital lesions is relatively common in genito-urinary tuberculosis. Although infection may spread within the genital system, or within the urinary system or both via the lumina of their ducts, that is, by direct extension, the co-existence of the disease may not be due entirely to direct extension from one to the other, as is sometimes stated. Coincidence of renal and genital lesions should be regarded as possible evidence of independent yet co-existing focal manifestations of the disease. The abundant arterial supply to the genital tract, the frequency of genital tuberculosis in the young adult, and the anatomical distribution of certain of the lesions would seem to favour blood-borne implantations.

Before the last war I believed that the only treatment for renal tuberculosis was nephrectomy in conjunction with sanatorium life for six months or a year. I considered that surgical removal of the tuberculous kidney was necessary to avoid the continued reinfection of the bladder below, and that when the ureter was involved, it should be removed along with the kidney. In a five-year follow-up of 30 cases of renal tuberculosis treated along these lines between 1935 and 1940 (Band, 1942), I had found that the operation deaths from nephrectomy were negligible and that the recovery rate was good as regarded the immediate future. But as the follow-up continued over a longer period, recurrence of bladder ulceration, reactivation of extra-urinary foci or persistent contracture of the bladder and consequent backward pressure on the remaining kidney began to take their toll. When a complete recovery was taken to mean complete rehabilitation of the patient and a return to employment, I found that the recovery rate of 86·4% in 30 nephrectomized patients was reduced to 50%, and that the ultimate mortality rate was 13·6%. When to the series of 30 cases of unilateral renal tuberculosis which were subjected to nephrectomy were added 11 cases of bilateral renal tuberculosis, the complete recovery rate fell to 36·5%, cases with residual disability amounted to 39%, and the late mortality rose to 24·5%. Of patients with bilateral renal tuberculosis, over 50% died within five years, even when treated under sanatorium conditions.

These pre-war figures were discouraging, but during the past five years, from 1950 to 1955, I have been able to observe the effects of chemotherapy in a series of 106 cases treated in East Fortune Hospital and subsequently followed up by re-examination at regular intervals.

Analysis of Cases

Sex incidence.—Of the 106 patients 74 were males and 32 females. Of the male patients 10 suffered from genital tuberculosis without associated urinary lesions; 40 males as compared with 21 females suffered from unilateral renal tuberculosis; and 12 males were, as compared with 7 females, admitted with the subclinical lesions of tubercle bacilluria. In my earlier investigation into the incidence of tubercle bacilluria I had noted that of 158 males examined in a sanatorium population suffering from extra-urogenital tuberculosis, 12·6% exhibited tubercle bacilluria, whereas of 142 females examined, 30·9% exhibited tubercle bacilluria. The recovery rate from tubercle bacilluria in both sexes was the same (23·4%) and the ultimate mortality rate in those patients with extra-urogenital tuberculosis and with tubercle bacilluria during those years (1930–1940) was high in both sexes (59%).

Age.—In the present series, the highest incidence of urinary tuberculosis occurred in the third, fourth and fifth decades in males and in the fourth decade in females (Table I). This is similar to the age distribution of pulmonary tuberculosis in the two sexes.

Table I.—Age Distribution

Decade	Males	Females	Total
10–20	5	3	8
20–30	20	7	27
30–40	17	14	31
40–50	25	5	30
50+	7	3	10
	74	32	106

Frequency of micturition as a symptom was taken as a frequency greater than three-hourly during the day and rising more than once at night. On admission, 58, or just over half the total number of patients, had frequency, and in all pus cells were present in the mid-stream or catheter specimen of urine. On discharge, 70% were symptom-free.

The total period of *bed-rest and hospitalization* is shown in Fig. 1 and it will be seen that most patients were given complete bed-rest for three to six months and remained in hospital for three to nine months. An adequate number of hours of rest in bed each day is an essential part of the hospital treatment, and the transition from complete bed-rest to a more active

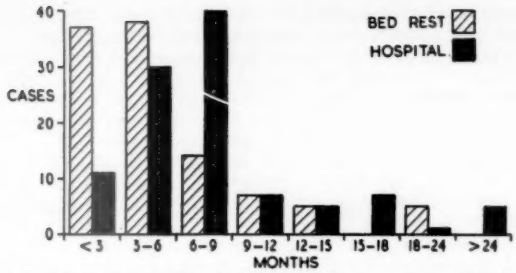


FIG. 1.—Total period of bed-rest and of hospitalization. Two patients transferred as bed-patients.

share in the social activities of the hospital is carefully graded. Any delay before admission to hospital has been due to delay on the part of the patient before medical examination is sought, and not to a waiting list.

The *operative interventions* undertaken in the entire series are shown in Table II.

TABLE II.—OPERATIVE TREATMENT

Nephrectomy	22
Nephro-ureterectomy	32
Partial nephrectomy	1
Uretero-colic anastomosis	4
Orchidectomy	2
Epididymectomy	1
Cordotomy	1
Excision of hydrocele	1
Cutaneous ureterostomy	1

In the *distribution of lesions* (Table III), 51 patients, or 53·6%, with renal lesions had associated cystitis.

TABLE III.—DISTRIBUTION OF LESIONS

	Males	Females	Total
Bacilluria	12	7	19
Restricted unilateral	6	2	8
Widespread unilateral	34	19	53
Bilateral	8	2	10
Residual cystitis	4	1	5
Renal with associated genital lesions ...	40	—	40
Renal with associated cystitis			51

Classification.—We have now adopted the following modification of the categories described by Jacobs and Borthwick (1950):

(1) Tubercle bacilluria without pyelographic evidence of calyceal ulceration.
(2) Restricted unilateral renal tuberculosis.
(3) Widespread unilateral renal tuberculosis.
(4) Bilateral renal tuberculosis.
(5) Persistent or residual tuberculous cystitis.
(6) Genital tuberculosis.

A follow-up system has been adopted which includes, for each category, the duration and variety of chemotherapy used, the duration of bed-rest and hospitalization, the length of time required to achieve conversion of the urine, the relief of symptoms of frequency, as well as the total period of treatment and observation required before the patient can return to employment.

(1) *Bacilluria.*—The total number of patients with bacilluria and no detectable renal lesion was 19. Of these, 11 of the 12 male patients suffered from associated genital lesions. About 25% suffered from a mild frequency of micturition. The time for conversion was relatively short (Fig. 2), and followed the pattern of the entire series. Similarly the delay before return to work after discharge followed the same general trend. The majority in this group had bed-rest for over three months and were in hospital for six to nine months. The duration of chemotherapy followed the general pattern and was continued for several months. Of the 11 patients with associated genital lesions, orchidectomy was carried out in 2 because of

widespread tuberculous epididymo-orchitis, and in a third patient hydrocelectomy was undertaken, though on histological examination of the thickened hydrocele sac evidence of tubercle was not found and at operation the testis and epididymis appeared normal.

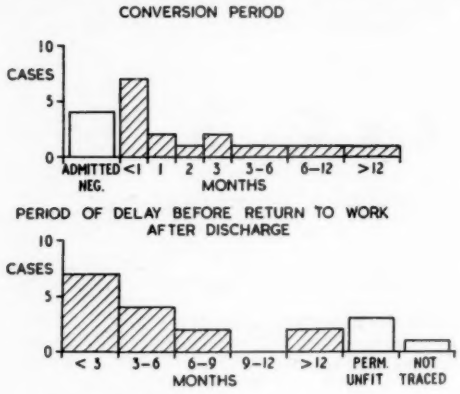


FIG. 2.—*Bacilluria:*

Total number of cases	19
Frequency present on admission	5
on discharge	1
Associated genital lesions	11

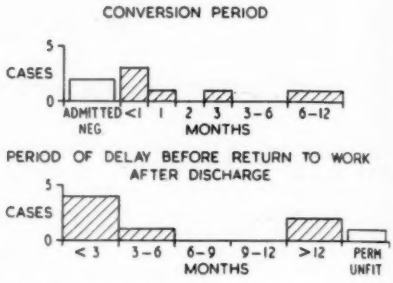


FIG. 3.—*Restricted Unilateral:*

Total number of cases	8
Frequency present on admission	3
on discharge	1
Associated genital lesions	3
Associated cystitis	3

(2) *Restricted unilateral renal tuberculosis.*—In this group there was a total of 8 patients. In 3 there was associated cystitis, and in 3 males there were associated genital lesions. The 3 patients with associated cystitis suffered from frequency on admission. In this small group, 6 of the 8 patients had conversion of the urine within a month of admission, and 5 of the 8 patients were able to return to work within six months of leaving hospital (Fig. 3). The duration of total bed-rest and hospitalization followed much the same pattern as in the whole series. Similarly, chemotherapy was given for a period of nine months to a year, including the continued administration of Pasinah for a short time after discharge from hospital. Nephrectomy was carried out in 2 patients and nephro-ureterectomy in one.

(3) *Widespread unilateral renal tuberculosis.*—This group of 53 patients was the largest in the series. Of these, 38, or 71·7%, had associated cystitis, and 19 of the 34 males (56%) suffered from associated genital lesions. Those with frequency on admission had cystoscopic evidence of tuberculous cystitis, and on discharge 9, or 24·3%, had some residual frequency. Although the disease was unilateral and widespread, the conversion period under chemotherapy was most satisfactory, and 46 of the 53 (86·8%) achieved conversion of the urine within three months. Of the 53 patients, 40, or 75·5%, were able to return to work less than twelve months after discharge from hospital (Fig. 4). Chemotherapy was used for a longer

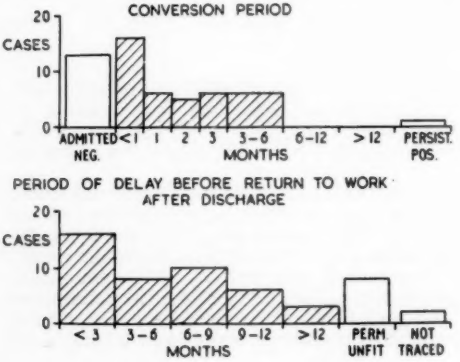


FIG. 4.—*Widespread Unilateral:*

Total number of cases	53
Frequency present on admission	37
on discharge	9
Associated genital lesions	19
Associated cystitis	38

period in this group, and 40 patients, or 75·5%, received such treatment for six to twelve months. In nearly one-third of these patients, chemotherapy was continued for a few months following discharge from hospital. The operation of choice was nephro-ureterectomy with two incisions, the first a sub-umbilical mid-line approach to mobilize the lower third of the ureter extraperitoneally and to divide it just above the bladder; thereafter the patient was turned on his side and the kidney and ureter were removed through a lumbar approach: the last rib was usually excised. Nephro-ureterectomy was performed in 27 patients, nephrectomy in 17, and in 2 a subsequent uretero-colic anastomosis became necessary. Operation was not undertaken when symptoms of genito-urinary tuberculosis were relieved by auto-nephrectomy after calcification, and when the extra-urogenital lesions were active.

(4) *Bilateral renal tuberculosis.*—This group included only 10 patients. Unfortunately the bilateral lesions occurred in a young age group, the majority males. In these young men associated genital lesions were common and in nearly all accompanied cystitis. All achieved conversion of the urine in six months, and 6 of the 10 patients were placed in some form of employment (Fig. 5). In 8 patients, complete bed-rest was continued for from six to nine

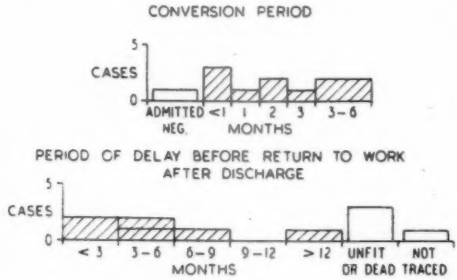


FIG. 5.—*Bilateral:*

Total number of cases	10
Frequency present on admission	8
on discharge	5
Associated genital lesions	6
Associated cystitis	8

months, and in 6 patients hospitalization was continued for as long as one to two years. In 8 patients chemotherapy was administered for nearly a year. In the operative treatment of these patients, the more seriously diseased kidney was removed in 7 cases. In 3 patients a persistently contracted bladder led to repercussions on the remaining kidney. Uretero-colic anastomosis of the remaining ureter was done in 2, and in the third patient, cutaneous ureterostomy, because of the extensive ureteric disease.

(5) *Residual cystitis.*—5 patients previously treated elsewhere for genito-urinary tuberculosis were admitted on account of reversion of the urine and recurrence of tuberculous ulceration of the bladder. 4 of the 5 patients again achieved conversion of the urine and a negative culture for tubercle bacilli. 3 patients were able to return to a modified form of employment within a year of discharge from hospital (Fig. 6). All had complete bed-rest for

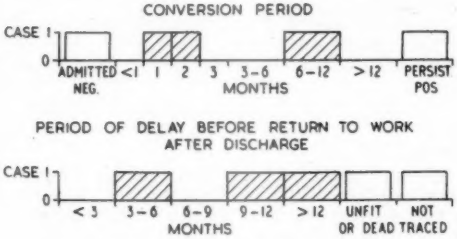


FIG. 6.—*Residual Cystitis:*

Total number of cases	5
Frequency present on admission	4
on discharge	1
Associated genital lesions	2

three months or less, and 4 were discharged in six months. The combination of bed-rest and chemotherapy was the treatment of the greatest value, and it was not considered advisable to attempt to apply diathermy to the solitary residual vesical ulcer. In 2 patients, bladder instillations of 5% isoniazid solution seemed to give some relief. Ureterocolic anastomosis for the remaining ureter was necessary in one case.

Still in hospital under treatment and therefore not included in this series is one patient with residual cystitis and stricture at the lower end of the remaining ureter for whom ureteroileostomy has been performed with success. A grossly dilated ureter and kidney have shrunk to normal dimensions and the intravenous pyelograms give evidence of good concentration. The blood urea has fallen to 50 mg. % from a figure which at one time reached 150 mg. %.

(6) *Genital tuberculosis in the male.*—Of all male cases reviewed, there were combined lesions in 41, or 55·4%, as compared with an incidence of 51·3% in the earlier series. In 10, or 13·5%, the lesion was confined to the genital organs. In 23 cases, or 31%, the lesion was confined to the urinary tract. These figures are comparable to those I had observed before chemotherapy was available, and the slight alterations in the percentages may be accounted for by more accurate personal observation and investigation. Furthermore, in the present series all examinations, cystoscopic, pyelographic or bimanual, have been made under Pentothal anæsthesia. In my earlier series bimanual examination under anæsthesia had not been carried out in every case, and involvement of the prostate, with irregularity in its consistence, had not always been detected.

In the present series, whereas involvement of the vesicle was noted in 64% of cases which was comparable with the incidence of tuberculous seminal vesiculitis in the earlier group, my records now show a marked rise in the incidence of tuberculous prostatitis, that is, 70% as compared with 17·8% in the earlier group observed. There was a relatively high incidence of a combination of genital lesions (34 patients, or 68%) (Table IV). In a certain number,

TABLE IV.—GENITAL TUBERCULOSIS IN THE MALE: DISTRIBUTION OF LESIONS IN 50 CASES

	Cases	Per cent
Epididymis	35 (8)	70 (16)
Seminal vesicle	32 (2)	64 (4)
Prostate	35 (6)	70 (12)
Combined genital lesions ...	34	68

(Figures in brackets indicate sole lesion.)

the pelvic genitalia, vesicle or prostate were alone involved. That the prostate and vesicle alone should be involved in 8 patients, or 16%, provides evidence of the possibility of a primary lesion in the pelvic genitalia in genito-urinary tuberculosis. 16, or 32%, of patients with genital tuberculosis suffered from tuberculous epididymitis with sinus formation in the scrotum, and I would like to stress the fact that out of 50 cases of urogenital tuberculosis in which the genitalia were involved, orchidectomy was considered necessary in only 2, and epididymectomy in only 1 patient. There can be no doubt that the scrotal lesion with sinus formation will heal under conservative measures alone. The response to chemotherapy, bed-rest with a scrotal support, and aspiration when necessary, is quite dramatic. In 34 of the patients (68%) there was conversion of the urine or of the discharge from the scrotal sinus in one month or less, and of all the patients with urogenital lesions, only one remained with a positive culture after treatment for six months (Fig. 7). This would appear to provide further support to the view that the treatment of genital tuberculosis should primarily be comparable to that of tuberculous pulmonary or osseous lesions.

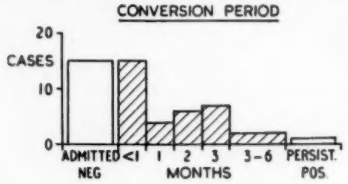
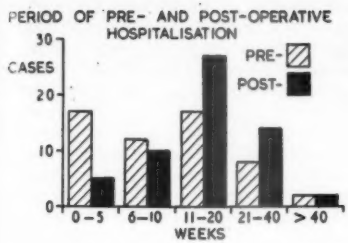


FIG. 7.—*Genital Tuberculosis in the Male:*
Genital without associated urinary lesions 10
Genital with sinus 16
Genital without sinus 34

TREATMENT

After admission to hospital, chemotherapy was given for a number of weeks in the period of pre-operative treatment (Fig. 8). During this interval when treatment was confined to bed-rest and chemotherapy, it was found that the majority of patients achieved conversion of the urine, and that culture for tubercle bacilli became negative. Thus in 90 patients there was conversion of the urine within three months of their admission to hospital (Fig. 9). The duration of post-operative hospitalization and of chemotherapy largely depended on the length of time it was considered necessary for the period of preparation, and this in turn on the degree of constitutional disturbance or the multiplicity of lesions. After discharge from hospital, patients were called for follow-up examinations at three-monthly intervals and were personally interviewed and examined by the consulting physician and surgeon together. A fresh specimen of urine was submitted for culture for tubercle bacilli, and at intervals the chest was re-X-rayed and a follow-up intravenous pyelogram carried out. Cystoscopy or retrograde pyelography was not repeated at the follow-up examination unless indicated by an alteration in the symptomatology, by pyuria, or by reversion of the urine to a positive culture.



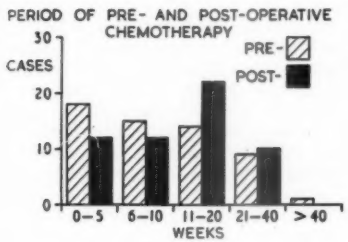
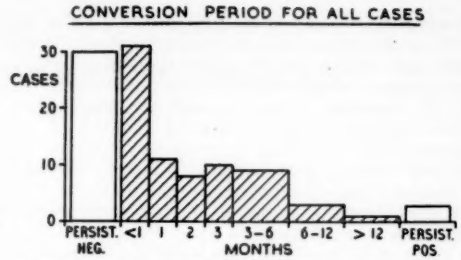


FIG. 8.



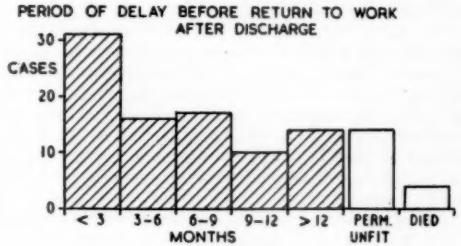


FIG. 9.

A closer collaboration between physician and surgeon in the treatment of genito-urinary tuberculosis has led to an increasingly frequent recognition of the presence of extra-urogenital tuberculous lesions, and in the present series these were found in 94% of cases. Patients with urogenital tuberculosis were accordingly notified as such and contacts were examined by the tuberculosis physician and his staff. It was considered advisable to inform the patient quite frankly that he was suffering from tuberculosis, and that he would ultimately benefit from the long-term follow-up which applied to all cases of tuberculosis, and so, from the beginning, patients were given training which was identical with that provided for the respiratory cases. They were impressed with the need for strict personal hygiene, and instructed in the handling of fomites and the observation of rest hours. There was a planned schedule of treatment which began with complete bed-rest, chemotherapy and operative intervention when necessary, and ended with rehabilitation and after-care. It was felt that patients with genito-urinary tuberculosis should be brought within the rehabilitation schemes already in existence for patients with respiratory tuberculosis, and should thereafter be helped to secure suitable employment without undue delay. In order to achieve this ideal scheme, arrangements were made to admit to East Fortune Hospital with equal priority those suffering from respiratory or genito-urinary disease. For the last four years, since there was no waiting list, immediate admission to hospital of all cases of genito-urinary tuberculosis became possible. Fortnightly supervisory, cystoscopic, or operative sessions were arranged, when the merits of individual cases could be discussed between physician and surgeon. Cases of urogenital tuberculosis were admitted to wards where open cases of respiratory tuberculosis were not normally treated, and it was considered that this segregation had considerable psychological value. The services of the almoner, Ministry of Labour officers, teachers and Local Authority nurses were made available to all. Social, economic and rehabilitation problems could be discussed and the patients were subjected to the same regular review and consultation with the tuberculosis physician as were the respiratory patients. They were also accustomed to the hours of rest and exercise which conformed with the general pattern of the hospital regimen. They entered into the social and recreational facilities of the hospital and were given week-end leave at three-monthly intervals.

Chemotherapy.—An increasing number of surgeons have now accepted the plea that chemotherapy should be administered not in a haphazard fashion but according to a definite plan carried out under sanatorium conditions. Five years ago, when the present series of cases was first observed, the chemotherapy consisted of streptomycin 1 gram with PAS 10 grams, daily for about thirty days, followed after an interval of a few weeks by another course, and later a terminal course of PAS alone. A year later, the superiority of uninterrupted chemotherapy was established, and moreover the problem of drug resistance was being met. Throughout 1952 the use of streptomycin was limited to 1 gram every third day, and the intensive course restricted to a few weeks. In the same year isoniazid became available and it was reported by the Medical Research Council that streptomycin used

intermittently was not entirely safe because of the development of resistance. Throughout 1953 continuous combined therapy with all three drugs—PAS, streptomycin and isoniazid—was used during the period of hospitalization. In patients older than 45 years, dihydrostreptomycin replaced streptomycin to restrict the incidence of vestibular damage. On the whole, however, it may be said that with these drugs chemotherapy has been remarkably free from toxic effects. Following the work of Dick (1954) who found that isoniazid-treated lesions appeared to heal by recapillarization whereas streptomycin-treated lesions apparently healed with a greater degree of fibrosis, PAS and isoniazid in full dosage have proved an effective chemotherapeutic combination, and PH(Pasinah), has been the drug combination of choice for continued use throughout the period of hospitalization and afterwards on discharge when the patient returns to his own home. Streptomycin, or dihydrostreptomycin, 1 gram daily, has been used without additional cover one week before and two weeks after the operative intervention.

We have considered it advisable to maintain out-patient chemotherapy for a varying period of months after discharge from hospital. This is done to cover the time during which a patient freed from the discipline of in-patient treatment must use initiative and restraint as a convalescent, in order to make progress towards rehabilitation. At this stage retrogression may occur, with reversion of the urine to a positive culture, if there is too much freedom and neglect of the regimen imposed in hospital. Pasinah, in the form of the combined cachet, is readily taken by the patient, and, as already stated, has latterly been the drug of choice for post-operative chemotherapy and follow-up domiciliary supervision by the patient's own doctor.

To particularize, the chemotherapeutic programme latterly has been as follows:

(1) PAS 16–20 grams and isoniazid 200–300 mg. daily, beginning at diagnosis or after the first group of three early morning specimens of urine have been submitted for culture.

(2) Streptomycin or dihydrostreptomycin 1 gram daily for seven days before and fourteen days after operation.

(3) Penicillin crystalline $\frac{1}{2}$ mega unit b.d. on day of operation and for six days thereafter.

(4) Vitamins A, D and C added to diet.

(5) Cachets of PAS and INAH combined (as Pasinah or Pycamisan) to provide a full dosage of 15 grams PAS and 200 mg. INAH. This treatment is continued for three months or longer, even up to one year, when there is evidence of chronic disease, genital or elsewhere.

Results

The clinical results of the past five years as compared with those of 1935–1940 have been amazingly good, and as far as we can judge they appear to be maintained. Relapses have been few, and attendance at the follow-up examinations has been almost 100%. When the patient attending at a follow-up clinic meets both surgeon and tuberculosis physician, all that is required of him can be dealt with at one session, and thus, by arrangement with the Tuberculosis Officer, the inconvenience of attendance at two clinics is avoided.

It has been found that these patients have appreciated the frank disclosure that they have become victims to tuberculosis, and that a hospital service is available which will provide all they require for treatment. Moreover, the instruction given to them by a tuberculosis physician and the talks they have had with almoners, Ministry of Labour officers and others, have assured them that while they are incapacitated it is possible for the family to continue at home, and that direction, or if necessary training, will be provided to ensure their return to suitable employment. They have accepted with confidence the prospects of a long-term course of treatment in which operative intervention looms no greater than a therapeutic incident.

We have been most impressed with the high percentage (83%) of our patients who have been able to return to employment within a reasonable interval after their discharge from hospital. The late mortality has fallen to 3·8%, and the number remaining permanently unfit reduced to 13·2%. When these figures are compared with those (24·5% and 39% respectively) of the smaller series of 41 cases which were personally followed up between 1935 and 1940, the contrast is remarkable, and a tribute to the efficacy of chemotherapy in tuberculosis.

REFERENCES

BAND, D. (1942) *Edinb. med. J.*, **49**, 273.
DICK, J. C. (1954) *Lancet*, ii, 516.
HAMMOND, T. E. (1941) *Brit. J. Urol.*, **13**, 43.
JACOBS, D., and BORTHWICK, W. M. (1950) *Proc. R. Soc. Med.*, **43**, 453.
MENVILLE, J. G., and PRIESTLEY, J. T. (1938) *J. Urol.*, **40**, 66.
MOORE, R. A. (1937) *J. Urol.*, **37**, 372.

Section of Comparative Medicine

President—Professor JAMES MCCUNN, F.R.C.S., L.R.C.P., M.R.C.V.S.

[*October* 19, 1955]

Liaison Between Two Professions with Similar Interests [*Summary*][1]

PRESIDENT'S ADDRESS

By Professor JAMES MCCUNN, F.R.C.S., L.R.C.P., M.R.C.V.S.

WHEN the Section of Comparative Medicine was instituted in 1924, mainly by the initiative and enthusiasm of Sir Frederick Hobday and Sir Clifford Allbutt, over 70 veterinary surgeons and a like number of medical men joined in the venture. Most of the members were drawn from the ranks of the clinicians who practised their profession in the field and were interested in the diagnosis and treatment of the diseases and abnormalities which confront a practitioner every day of his life. I expected to gain much from the meetings for there is a great extent of common ground between the practitioners of the medical arts and science.

This common ground has been recognized for a long time. The earliest physicians attended to man and animal and the cleavage occurred only when the doctrine that man was the possessor of that divine attribute, a soul, was accepted. This placed animals on a lower plane and the ancient physicians gave them attention no longer for fear of debasing their profession. It took many centuries to regain the lost ground and the repercussions of the doctrine were felt in both fields and probably most harm was done to the forward progress of human medicine, for, as man possessed a soul, his body was sacred and even dissection and investigation *post mortem* were prohibited. The coming together of the two disciplines and the recognition again of a common ground was exemplified best in the late eighteenth and early nineteenth century when the veterinary profession, as we know it to-day, was going through the pangs of birth and the mediæval conceptions and ideas were being cast aside.

We of the veterinary profession will ever be grateful to those medical men, M.R.C.S.'s and L.S.A.'s who joined our ranks and by virtue of their more specific training and scientific outlook laid the foundations on which a learned profession could be built. I will mention some of them, for we hold their names in great honour—Delabere Prichett Blaine, Moorcroft, Bracy Clark, William Percival and Joseph Goodwin. There were others who helped by allowing veterinary students access to their classes and by acting as examiners—E. Wilson, Abernethy, Hume, Travers, Cruickshank, Lister, Bell, Brodie, Bransley Cooper, Jolly, Quain, Fordyce, Barley Babington and Bright.

Edward Coleman, the second Principal of the Veterinary College (1794–1839) was a surgeon but there is some debate, to which I do not entirely subscribe, as to whether his influence, during his long reign of nearly fifty years, was a good one. John Hunter, Henry Cline and Astley Cooper took an active part in the foundation of the Royal Veterinary College. John Hunter was a profound student of Natural Science. He practised in the human field but he could have won equal renown had he devoted his efforts entirely to veterinary science.

It is said that Moorcroft approached Hunter for advice as to whether he should take up veterinary science as a permanent calling. Hunter said "If I were younger I would take up veterinary science forthwith". Here also is what Quain said in 1863: He could not see why there should not be the greatest sympathy between the College of Veterinary Surgeons, the College of Physicians and the College of Surgeons. Their anatomy was very nearly the same, their physiologies were quite identical, their pathologies were identical and the practice of one harmonizes very much with that of the other so that he did not see why there should not be the greatest sympathy between them.

Again on the same occasion Dr. Sharpey said "Physiology is the same in both cases. Let me observe that we are largely indebted for the progress of physiology as a general science having no more special reference to man than to domestic animals, on which we so much depend, to members of the veterinary profession".

There can be no doubt that some of the medical men who joined the veterinary profession did so for purely altruistic motives, others did so because they recognized that their training and skill would command greater reward in the new field. Moorcroft who established his veterinary practice at 224 Oxford Street made a fortune in 16 years, and then in 1808 went to India as veterinary surgeon and adviser to the East India Company at £3,000 per year.

[1]The full paper will appear in the *British Veterinary Journal* for February 1956.

The medical men who helped at the beginning were recruited mainly from the ranks of the surgeons. The physicians were very superior beings and they would not deign to pay attention to the diseases of the lower animals. On those occasions when they were asked by the government to give their views on epizootics such as cattle plague and foot-and-mouth disease they said that they would do so only from a sense of duty to the nation and apologized for debasing their profession. It would have been better for the nation if their sense of duty had not been so strong and they had remained silent. Their ignorance was abysmal and especially so of the natural history of contagious disease. As some excuse one must remember that the ancient notion of the spontaneous origin of disease was not refuted completely until the latter part of the nineteenth century.

Professor J. B. Simonds who was Principal of the Royal Veterinary College (1871–1881), veterinary surgeon to the Privy Council and adviser on veterinary matters to the Government, did not accept completely the contagion theory until 1875 when Professor Brown (later Sir George T. Brown) by experimental proof was able to convince him of the contagious nature of pleuro-pneumonia in cattle. It is said that Simonds held that the liver fluke was of spontaneous origin and was the result of, and not the cause of, the liver disease with which it is associated.

It is strange that the theory of spontaneous origin was held so strongly and for so long, even until late in the nineteenth century, by competent and eminent men of the medical and veterinary professions.

Primitive people in Africa had long recognized that pleuro-pneumonia of cattle was contagious. In 1795 Thomas Peall had demonstrated at the Veterinary College that glanders could be transmitted from one animal to another; he took material from a farcy ulcer and smeared it on the nasal mucous membrane of an ass; the ass became glandered on the eighth day. In 1854 John Snow had traced a cholera outbreak to the Broad Street pump.

Undoubtedly the veterinary profession owed much to the medical profession in the eighteenth and early nineteenth centuries and when one considers the great number of surgeons and physicians who contributed freely to the literature and so added to the store of knowledge on matters appertaining to animal husbandry and disease and, in many cases, abandoned their human patients in order to devote their whole time to veterinary science, the integration between the two branches of medicine must have been very great at that time.

Medical men played a great part in the founding of the Veterinary College and in its subsequent management. No doubt they recognized that the time had come when a systematic course of training, with requisite test of efficiency, should be available for the better education of those who desired to follow a career in veterinary science. There was a properly constituted Veterinary College, in which all known facets of veterinary art and science could be studied, before there was a Medical School or College in London which could provide within its precincts similar facilities for a potential doctor.

At first the students resided at the Veterinary College and, according to the regulations then in force, they lived a spartan life rising at 6 o'clock in the summer and 7 o'clock in the winter and they were required to retire to their bedchamber at 10 p.m. They were not permitted to burn a candle in the night under the pretence of study. Lights were to be extinguished before the pupils went to bed and none was to remain up after eleven o'clock. The daily period of study concluded at 7 p.m. Prospective students had to submit evidence of a good education and be between the ages of 15 and 22. Preference was given to those who had some knowledge of surgery and pharmacy and the limitation of age did not extend to practitioners in medicine and surgery. The course was a comprehensive one including zoology, botany, anatomy, physiology, pharmacy, pathology, shoeing and attendance in the infirmary and at operations.

It was considered that a term of three years was sufficient to complete the students' education provided that they were capable, assiduous and well inclined.

No doubt the medical men who were interested in the advancement of veterinary science had a hand in the designing of this curriculum which was in many ways in advance of that followed by medical students in 1791.

I regret to say that this brilliant conception was brought to naught by a medical man.

The first Principal, Professor St. Bel, died in 1793 and a young surgeon, Edward Coleman, a protégé of Hunter and Cline, was appointed in his stead. He took office in 1794. Coleman, unlike the other medical men who had transferred their attention to veterinary science, was completely ignorant of any veterinary knowledge. It is said that his sole claim to authority lay in the fact that he had dissected and described a horse's eye.

His appointment was not received well by those who had veterinary knowledge and especially by those with medical qualifications and he met with much opposition. Safe in the post, being sponsored by J. Hunter and Cline, Coleman sought for the means to thwart opposition. He advised the governors that it was not necessary for a veterinary student

to be well educated, that grooms and kennelmen would make the best veterinary surgeons and that the sons of doctors made the worst; there was no need for such a long course of study and a few months would suffice. His advice was accepted and subsequently he passed them through his training mill in three months. The College ceased to be residential and hordes of students passed through its portals and were awarded their diplomas. It was not long before Coleman could command a strong following in the profession and he was able to reign and command like an autocrat.

It is strange that the great ideals on which the College had been founded, largely due to the initiative and foresight of sagacious medical men, should have been sabotaged by one of their order. The clock of progress was put back by well over half a century. Coleman was an able man and of nimble wit in his own interest, and one cannot deny that in the course of time he did make many additions to the sum of veterinary knowledge.

Here are extracts from the reports on two of the many experiments that Coleman made whilst investigating natural and suspended respiration. Coleman was a keen investigator and his powers of observation were acute. His book entitled "Dissertation on Natural and Suspended Respiration" was published in 1802 and dedicated to Henry Cline. It is interesting and instructive even now.

(1) "A cat was strangled, and five minutes after the last expiration the chest was opened; the lungs were then alternately expanded and collapsed for five minutes, the heart acted rather powerfully, but no alteration could be observed in the blood of its two sides; either as to quantity or quality. " The heart was now electrified by small shocks, during the existence of the collapse, and this was continued for five minutes, when, upon examination, it was observed that its action was evidently lessened; the left side became rather more distended than before, but the blood was black in both auricles and ventricles.

" The lungs were now expanded, and the heart at this instant electrified: after two shocks had been given, they were collapsed, again expanded and electrified; and this process likewise was continued for five minutes. On examining the heart, both sides were now found less distended, their action quickened, and the blood in the pulmonary veins, left auricle and ventricle, completely florid.

"The result of this experiment not only proves the advantages of the stimulating power of electricity on the heart, beyond that of simple inflation, but also evinces the superiority of administering it in the distended, over the collapsed, state of the lungs."

(2) "A cat was strangled; and after it had ceased to breathe, the body and extremities were thoroughly rubbed for ten minutes, the chest was then opened. On examining the heart, the right side was found fully distended, and the left rather more so than usual, without any sign of action in either.

"An opening was then made in the inferior cava, so as to let out a portion of blood; and the action of the right side of the heart was soon renewed.

"This experiment was repeated, and it invariably resulted that the more the right side of the heart was distended the weaker was its action, and, even where no action was evident during the distension, it was generally renewed by removing part of the blood from the anterior cava."

Coleman resisted all attempts at reformation and particularly so if those projects were sponsored by men who were products of the original three-year course or had medical qualifications. I am afraid that there was little integration in this country again between medical men and veterinary surgeons until 1871 by which time Coleman and his two successors, Sewell and Spooner, had departed this life.

The years between 1800 and 1871 wilted under E. Coleman's autocracy and the complacency and vacillation of his successors, Sewell and Spooner, but they were not completely sterile. In spite of the lowering of the preliminary educational standards and the debasement of the course of training, some good men were produced who kept the torch of truth and knowledge glowing.

When the Veterinary College was established rules and regulations were ordained for the conduct of affairs. Regulation XVII stated: There shall be chosen, on the day of election each year two committees viz: A Medical Experimental Committee and a Committee of Transaction.

John Hunter was appointed Chairman of the Medical Committee and amongst the members were Mr. Cline, Mr. Vaux, Sir George Baker, Dr. Packwood, Mr. Peake and Mr. Horne and Mr. Sheldon. These were all men of medical renown and Regulation XIX specified the duty of that committee.

> "The Medical Experimental Committee shall meet occasionally for the purpose of suggesting and trying experiments with a view to throwing additional light on animal economy and to discover the effects of medicines upon different animals to be procured for that purpose; and this Committee shall from time to time make reports of their proceedings to the Council."

It will be seen that the men who promulgated such a regulation were men of vision who anticipated rightly that the Veterinary College would become a great centre of learning and for the dissemination of knowledge. It might have been so from the earliest days if Coleman, probably to cover his own ignorance, had not drawn the veil of secrecy over the work of the institution. He opposed all efforts for reform, he refused to train his students on any animal other than the horse. He did not welcome veterinary surgeons into the College and refused to have them on the board of examiners. In all this stupidity he was supported by his friend Astley Cooper. I doubt if J. Hunter would have succumbed to his persuasion. His conduct led to a justifiable reaction in the profession and this was made manifest in the columns of the "Veterinarian" under the Editorship of Wm. Youatt, who was veterinary surgeon to the Zoological Society, and by Bracy Clark, a very competent practitioner, in the "Farrier and Naturalist" and later in the "Hippiatrist."

These periodicals helped to save the situation for the members of the profession, outside the College, did not accept or follow the code of secrecy.

Many books and pamphlets dealing with the diseases and economy of the domesticated animals were published by veterinary surgeons and medical men. One can read to-day, with pleasure and profit, the articles and communications of such men as Percival, Blain, Youatt, Bracy Clark, Lawrence, Castley, Gamgee and Barlow.

During the first half of the nineteenth century, largely owing to the stupidity of Coleman and his medical board of examiners, who looked upon veterinary surgeons as inferior men, relations between the two professions were not ideal. Medical men were consulted and appointed to government committees of enquiry into the cause and prevention of epidemic diseases of animals to the exclusion of veterinary surgeons. The advice of competent and experienced veterinary surgeons was ignored and with disastrous results, especially in the case of cattle plague which ravaged the country periodically.

All things come to an end and when Simonds became Principal of the Royal Veterinary College on the death of Spooner the school entered upon a new birth. He expanded the curriculum to include the other important domesticated animals. He provided better facilities for the teaching of anatomy, physiology, pathology and chemistry, and although in his official duties as veterinary adviser to the Privy Council and Government his wise counsels on the control of epidemic diseases were often discarded in favour of those given by medical men, still the seed of better relations between the two professions was sown.

A study of the list of the teachers at the Royal Veterinary College in the late nineteenth and early twentieth century reveals the names of medical men of fame. T. S. Cobbold, D'Arcy Power, Henry Power, T. G. Brodie, George Buckmaster, Legge Symes, Marrett Tims and W. B. Bottomley. These men gave great service to the College and did much to show that medical men and veterinary surgeons belonged to one great science and on equal terms. The same type of amicable collaboration was witnessed in other veterinary schools, medical men undertaking much of the teaching in the preclinical period. The names of Macdonald and Roaf of Liverpool, Lindsay of Glasgow and Dryerre of Edinburgh come to mind and these men are held in high regard by the veterinary surgeons who sat at their feet.

The list of the men who have given valuable assistance to the R.C.V.S. at the examinations leading to the diploma of membership would make a medical Debrett.

In the latter half of the nineteenth century when Pathology claimed a rightful place in the curriculum and especially when Bacteriology entered upon its golden days, a great new field of common interest was opened up. It is in this field that integration between the two professions was at its best, for the majority of the workers were qualified medical men or veterinary surgeons. Two men did more than any others to bring about this fusion of interests: Sir John MacFadyean on the veterinary side and Professor William Bulloch on the medical side.

As academic knowledge of the nature of disease processes and the cause thereof accumulated, other workers were able to put it to practical application in an effort to solve and resolve problems of public health and preventive medicine. Prime workers in this field on the medical side were Delépine, Sims Woodhead, Leighton, Savage and, in recent years, Dalrymple-Champneys; on the veterinary side the names of Walley, Stockman, Brittlebank, Hayhurst, Malcolm and De Vine come immediately to mind.

Up to this point, which carries one well into the present century, progress in medical and veterinary science, with a few exceptions such as Pasteur, was effected through the efforts of men who were qualified to practise those sciences if necessary in the field. No man can be an expert in all fields and it soon became evident that if progress was to be made he should know more and more about a little and less and less about a lot.

There was only one answer, specialization, and this meant also that men qualified in other disciplines such as chemistry, biochemistry, physics, zoology, &c., had to be called in.

In this Address I have attempted to show how the two professions of Medicine and Veterinary Surgery were allied at the time of origin of the veterinary profession in this country, and that we have much in common in our daily work and our educational problems.

Section of the History of Medicine

President—Sir Zachary Cope, M.S., M.D., F.R.C.S.

[*November* 2, 1955]

The Indian Medical Service. A Short Account of its Achievements 1600 – 1947

By Donald McDonald, B.M., F.R.C.S.Ed.
Lt-Col. I.M.S. retd.

When, on December 31, 1600, Queen Elizabeth granted a charter to the Association of Merchant Adventurers of London, to trade with the East, the East India Company was born. The establishment of the Company came at the end of a long struggle between the nations for the control of the lucrative spice trade, in the course of which first the Venetians, then the Portuguese, the Spaniards, the Dutch, the French and, finally, the British were drawn into that vast treasure hunt. How lucrative a trade this was is shown by the fact that, in 1580, cloves gathered in the Moluccas were being sold in London for eight hundred times their cost.

The British started late upon this enterprise and, in an attempt to circumvent the mighty hold of Spain and Portugal upon the western and eastern approaches guarding the Spice Islands, their first ventures were made from the North West. But, even before the defeat of the "Invincible" Armada had opened up to both Dutch and British vessels the route by the Cape of Good Hope, Sir Francis Drake had, in the course of his voyage round the world, in 1577, touched at the Moluccas and arranged with the King of Ternate to take up on behalf of England the whole of the clove production of that island.

The first fleet of the Company sailed under the command of Captain (later Sir James) Lancaster, in December 1600, with "foure tall ships"—each of which carried "Surgeons twoe and a Barber"—men who, though otherwise completely unknown to fame, were destined to be the forerunners of that long line of European and later Indian, doctors who, during the last three and a half centuries, have given their services, and often their lives, to the East—first with the Company then, after their formation in 1764, with the three Presidencies of Bengal, Bombay and Madras and, finally, with the Indian Medical Service into which the Presidency Services were amalgamated in 1897. When that Service came to an end, on August 15, 1947, with the transfer of power to the two Dominions of India and Pakistan, the grand total of all regular officers who had so served since 1600 amounted to 6,932, of whom 404 were Indian and 6 Burmese.

In the early days of the Company the doctors went with the traders to the founding of the factories, and were often of great assistance, by virtue of the medical treatment which they could offer to rulers from whom concessions were required. There was, for instance, Gabriel Broughton, Surgeon to the ship "Hopewell" who, in 1636, attended the daughter of the Great Moghul—the Emperor Shah Jehan—who had sustained severe burns by her clothing catching fire. Broughton, on being asked to name his reward, sought for no private emolument but solicited that his nation might have liberty to trade free of all duties with Bengal, and to establish factories in that country.

Again, when an important embassy went from Calcutta to the Emperor, Farekh Siyar, in 1714, it was the skilful treatment of the Emperor by the Company's Surgeon, William Hamilton, a cadet of the family of Hamilton of Dalziel, that eventually obtained important concessions upon which the subsequent prosperity of the Company largely depended. The Surgeon, John Zephaniah Holwell, grandson of John Holwell who was at one time Astronomer Royal, held office in Calcutta in 1756, when Suraj-ud-daulah laid siege to and captured that city. The Governor having deserted his post, Holwell took command of the garrison until he was compelled to surrender it and afterwards to endure, with his companions, the night of agony in the Black Hole. Holwell subsequently served on the Council and, when Clive resigned, held the Governorship of Bengal for six months. He was the second officer of the Service to be elected Fellow of the Royal Society. He died at the advanced age of 87—in itself a remarkable achievement considering what he had survived.

The earliest Fellowship of the Royal Society awarded to a Surgeon of the Company went to John Fryer, described in the records as "a skilful and experienced artist in his profession". Fryer had travelled extensively, and his "New account of the East Indies and Persia", published in 1681, is still a valuable guide to the customs prevailing in those countries at that time.

But, in the seventeenth and early eighteenth centuries, the orderly and well-behaved surgeon was the exception. There was, for example, a certain Mr. Cunningham, in 1704, the first of a long line of Service naturalists who, "though he was bred a surgeon had turned Virtuoso and would spend whole Days in contemplating on the Nature, Shape and Qualities of a Butterfly, or a Shell-fish, and left the Management of the Company's Business to others as little capable as himself, so everyone but he was Master".

One man, however, in the service of the Company at that time, though he himself never went to India, exercised considerable influence upon the practice of western medicine in the East. John Woodall was appointed, in 1613, as Chirurgeon General to the East India Company. He had already served as Surgeon to Lord Willoughby's Regiment in 1591 and, thereafter, spent seven years in Germany, Poland and France. In 1616, the year in which Dr. William Harvey delivered there the first of his lectures on the circulation of the blood, Woodall was elected Surgeon to St. Bartholomew's Hospital. In 1633 he became Master of the Barber Surgeon's Company. He published, on behalf of the Company, directions regarding the preservation of health on board ship in his "Surgeons Mate" (1617)—a book which is, in its way, a minor classic for, though guides to military surgery had been in use for some time, there had been no previous manual written especially for the use of ships' surgeons. Woodall's observations regarding scurvy show that he was well in advance of his times. He insisted upon the use of the juice of oranges, limes and lemons on board ship over one hundred years before James Lind published his "Treatise on the Scurvy" (1753), which eventually led to the adoption of lime juice as a routine on all ships of the Royal Navy.

During the two and a half centuries in which the Company maintained their eastern trade, they were under the constant necessity of maintaining, also, a considerable service of vessels for transportation of merchandise and for conveyance of their servants to and from the eastern settlements. Those vessels had, in addition, to serve the purpose of defence, not only against the forces of Spain but, also, against the innumerable pirates which infested the seas. Life on board an Indiaman in those days was, indeed, no bed of roses. "Why, Sir," as Doctor Johnson so succinctly put it, "no man will be a sailor who has contrivance enough to get himself into a jail." Voyages took many months and, unless the Surgeon of the vessel settled down well with the Commander, his life was a poor one. It is on record, for example, that Andrew Trumball, Master of the "Hopewell", in 1643, admitted chastising his surgeon with a rope's end. However, in spite of the manifold disadvantages of the Sea Service of the Company, many men who subsequently attained to considerable eminence were not averse to entering it. One of the best known was the African explorer, Mungo Park, who served as Surgeon's Mate from 1792 to 1793. The merest chance prevented the poet Keats from taking service with the Company. In 1820, the fear of poverty, the onset of tuberculosis and the unfavourable reception of his work by the public, all united to make him search desperately for some alternative way of life. His early training as a doctor offered the obvious choice, and a letter included in Houghton's life of the poet contains this extract: "I have my choice of three things, or at least two—South America, or Surgeon to an Indiaman, which last I think will be my fate. I shall resolve in a few days."

Possibly the most remarkable career of any medical officer in the Sea Service was that of Sir Robert Mac Ara who, while serving as Surgeon to several Indiamen, at the same time held a combatant commission in the British Army. Though the first twenty-one years of that service were nominal, Mac Ara was gazetted, in 1803, as Captain in the 42nd Foot—

the Black Watch—saw service in the Peninsula and elsewhere and, eventually, fell at Quatre Bras, in 1815, commanding one of the finest regiments in the British Army in the greatest campaign in which that Army had ever been engaged prior to 1914.

By 1764 the Company were so well established that regular medical services could be constituted in the three Presidencies, with fixed grades and definite rules for promotion. An attempt was made, too, to recruit a better average type of doctor for, though the day of antiseptics and anæsthesia was still afar off, the general status of the profession had greatly improved. A hospital had been erected in Madras as early as 1664, and another in 1688, during the Governorship of Elihu Yale who, later, gave large donations to the school at New Haven in America which, in 1745, developed into the great University which bears his name. Bombay had its first hospital in 1676 and, by 1700, there were three hospitals in Madras. A third hospital was erected in Bombay in 1784 but building did not commence in Calcutta until the eighteenth century—the first hospital being opened there early in 1708, concerning which the traveller, Alexander Hamilton, wrote: "The Company has a pretty good hospital at Calcutta, where many go in to undergo the Penance of Physic, but few come out to give an account of its operation." By the end of that century, however, the Calcutta Native Hospital had been opened and three others were in existence in that city.

The remuneration of a surgeon in the eighteenth century was not high. In Bombay, where it was higher than in the other provinces, a senior surgeon could command as much as £90 per annum, but by 1729 that sum had been reduced to what must seem to have been their current market rate, £36 a year. There were, however, three sources from which a surgeon might supplement his income. He might be fortunate enough to secure one of the few really lucrative appointments, such as the Residency Surgeoncy at Lucknow, which carried allowances paid by the Vizir of Oudh for attendance upon his family: he might participate in the issue of prize money; or he might frankly and unashamedly indulge in trade. Many considerable fortunes were built up at that time, not from professional earnings, still less from official pay, but from contracts and trading. An early instance is found in the career of an Indian Assistant Surgeon who, by his death at the age of 97, had accumulated more than £130,000, mostly by judicious investment in land and country produce. But, by a General Order of 1826, commercial speculations were forbidden to all officers of the Company, and those practices gradually came to an end. It is not generally known that Oliver Goldsmith, who studied medicine at Edinburgh and on the Continent, and took a medical degree either at Louvain or at Padua, was once tempted by such prospects. He had been promised the gift of a post as Surgeon to a factory on the Coromandel Coast, where it was said that he would receive £100 a year, with the expectation of a further £1,000 from private practice. He was, however, found medically unfit to join.

Quite apart from their excursions into trade, the Surgeons of the Company were frequently employed on activities outside the practice of medicine. Many were distinguished naturalists, who studied and wrote about the Botany and Zoology of India, while others were among the first to study the languages and religions of the East. James Anderson introduced cochineal into India and played a large part in the introduction of silk, sugar cane, coffee and American cotton. The use of lac dye was discovered by another surgeon, David Turnbull. Others made extensive travels—among them Alexander Hamilton, whose views on the Calcutta Hospital have been noted above. Hamilton was one of the first Europeans to visit the forbidden city of Lhasa. John McNeill, profiting by his knowledge of Persian, entered the diplomatic service, where he rose to become Minister Plenipotentiary to the Shah from the Court of St. James, and eventually Privy Councillor.

Medical Officers took part in the foundation of other departments in the organization of Government. Sir William O'Shaughnessy, while serving as Professor of Chemistry at Calcutta, conducted the first experiments for the introduction of the Electric Telegraph into India, and became Director General of Telegraphs in 1852. In 1861, James Rankin was appointed as Director General of Post Offices in India. John Forbes Royle represented the Company as Reporter on their Economic Products at the Great Exhibition of 1851, while the first four appointments as "Conservator of Forests" were filled by medical officers.

In the field of philology the achievements of the Company's Surgeons were remarkable. John Leyden, after studying at Edinburgh, was licensed as a preacher in the Church of Scotland in 1798. He became interested in the East through reading about the travels of Mungo Park and, being offered an appointment in the Indies if he could secure a medical qualification, accordingly, in 1802, and after only six months study, obtained both the L.R.C.S. of Edinburgh and the M.D. of St. Andrew's. After three years in India he was appointed Professor of Hindustani at Calcutta. Two years later he was Judge and Commissioner of the Court of Requests and, the next year, Assay Master of the Mint. In 1811 he accompanied the Governor General to Java as his official interpreter. Among other works on the science

of languages, Leyden compiled grammars of Malay and Prakrit and, after only eight years of service, translated the Gospels into such unusual tongues as Pushtu, Baluchi, Maldivian, Macassar and Birjis. He died at the age of 36, of a fever contracted whilst examining manuscripts in a damp ill-ventilated room. Horace Wilson, who spent almost his entire service as Assay Master to the Calcutta Mint, published more than thirty works on eastern languages and was, after his retirement, appointed Boden Professor of Sanscrit at Oxford. The most remarkable of these intellectual giants, however, was an Austrian, Aloys Sprenger, who joined the Service in 1842. Sprenger devoted his whole service to the study and teaching of languages of which he was reputed to have known twenty-five. After retirement, he was elected Professor of Oriental Languages at Berne.

In 1858, the Crown took over the Government of India and, with the great developments in the art of medicine which were occurring, the Service entered upon a new phase of its history. Owing chiefly to the philanthropic and unselfish work of John Howard, the great prison reformer of the eighteenth century, conditions in the hospitals of Europe had undergone drastic reforms and India benefited from the effects of the improvements introduced. The building of the great General Hospitals in the Presidency towns was commenced, and many smaller hospitals and dispensaries were established in the districts. In 1835 a Medical College was founded at Calcutta and another at Madras. Ten years later a College was instituted at Bombay. From 1853 onwards, numerous medical schools were founded by the enterprise of medical officers of the Service for the instruction of doctors entering the subordinate grades—schools which were manned by them entirely until such time as they had trained graduates to succeed them. Of officers willing to undertake this work there was never any lack, and it was not long before a flood of qualified doctors, trained in the practice of western medicine, began to pour out from those institutions to meet the growing need for modern medical treatment throughout the Provinces of India. The name of many an officer who taught during those earlier years is even now mentioned with affection and respect by some old greybearded practitioner, long after the officer himself has gone from the country and been forgotten by the rest of India. Yet it has been the often meagrely rewarded labours of those forgotten men, extending over many years, that have made possible the great step forward that was taken by the indigenous medical profession in India during the last hundred years.

The Indian Medical Service had, however, always been primarily a military service—a reserve to provide medical officers for duty with the Indian Army in time of war and, from the middle of the eighteenth century onwards, the Company was almost continually at war. France and England fought in Europe, and India took its share in that struggle from 1745 to 1748—a struggle which, under the pretext of supporting various Nawabs and Rajahs, was continued in India for a matter of another fifteen years. Those operations meant the constant maintenance of armed forces which, in four Mysore Wars and two Maratha Campaigns, had plenty of practice in the exercise of their profession. In every war, and in every frontier expedition in which the Indian Army was engaged, from Hunza and Nagar on the North West border of Kashmir down to Ceylon, and from China to Arabia, members of the Indian Medical Service, as an integral part of the Indian Army, have played their part. They were to be found, also, in Africa, from Egypt to the Cape of Good Hope. Four men, who afterwards joined the Service, served in the Peninsula, three at Waterloo, and twenty-five in the Crimea. In short, in every war of any importance, in which the British Army was engaged during the nineteenth century, except in the final advance on Omdurman, members of the I.M.S. have served. They were not absent even from the American Civil War, the Franco-German or the Russo-Turkish Wars. From the treacherous attack upon our troops during the retreat from Kabul in 1842, the sole survivor out of a force of 31,000 men was Assistant Surgeon William Brydon, who was again wounded during the Mutiny—that time while sitting at dinner in the Lucknow Residency. His tragic return from Kabul was finely depicted by Lady Butler in her picture "The Remnants of an Army".

During the 1914–1918 war, the Service was represented in France, Flanders, Palestine, Asia Minor, Transcaucasia, Persia, China, Aden, East and West Africa. 92 retired officers rejoined for duty, and over 1,000 temporary commissions were granted. During the Second World War, over 1,000 Field Medical units were mobilised, in addition to hospital accommodation for 11,000 officers and 150,000 other ranks arranged for in India. In the course of all these various campaigns the Victoria Cross was earned five times. One of the recipients, John Alexander Sinton, was later awarded the Fellowship of the Royal Society for his researches into the problems of malaria—a unique combination of honours.

The following tribute from General Sir Neville Chamberlain, written in 1887, will show how the work of the Service appeared to an administrator of that perpetually troubled district—the North West Frontier.

"You are right", he wrote, "in supposing that I have expressed an opinion that the peaceful and civilizing influence of the work done in the dispensaries and by the regimental surgeons on the frontiers of India, has been in political importance equivalent to the presence of some thousands of bayonets. I have held this opinion because no amount of military coercion, or of purity of administration could have exercised the same pacifying effect on the heart of the natives that has been produced by the sympathetic care and successful treatment of diseases, many of which had been previously considered incurable. Throughout my service I have never known a time when the halt, the lame, and the blind have not flocked into our cantonments, or into our camps in search of relief from suffering; and, however distasteful may have been the sight of our soldiers, or however galling the idea of subjection to British rule, the people have come with confidence from far and wide to seek medical aid. The fame of the English doctors has spread beyond our frontiers into the remotest hills and glens, and the difficulties overcome and the sufferings endured in order to reach a medical officer might seem incredible to those unable to realise what it is to be living under conditions devoid of medical and surgical aid."

Unfortunately those facts were not always appreciated by those who had best reason to know their truth. In the Legislative Council in Delhi, in 1918, a motion was brought forward by an Indian Member of the Council to disband the I.M.S.—chiefly on the grounds that India was a poor country and could not afford the pay necessary to maintain such a Service. The spirited defence put up by Surgeon General Edwards sums up graphically the achievements of the Service at that time and its justification for continuance.

"I need not dwell", said General Edwards, "on the fact that this resolution is tantamount to the abolition of the distinguished Service to which I have the honour to belong, but before proceeding with my reply I wish to say a few words concerning the work which has been done by this Service in recent years, and which is still being done, for I do not think that this Council is fully aware of the extraordinary value of the Indian Medical Service, not only to India but to the world at large. . . . This Service has worked out the life-history of the malarial parasite, a discovery which has revolutionized our ideas concerning malaria and which, among other things, has enabled the Panama Canal to be successfully built. It has reduced the mortality of cholera by two-thirds and shorn amœbic dysentery of most of its terrors. It has worked out the method of transmission of bubonic plague, work which points the way to the ultimate eradication of that disease. Enlarged prostate, that terrible and fatal concomitant of old age, can now be overcome, thanks to a member of the I.M.S., while in the domain of eye surgery, more especially with regard to cataract and glaucoma, the work of the Service is recognised throughout the scientific world. . . ."

Fortunately the Service weathered that storm, and was able to continue for a further thirty years its beneficent work in research and the unending problems of public health—achievements by which it is well content to be judged at the bar of history. Great names, indeed, there have been in recent years—Ronald Ross, Leonard Rogers, Rickard Christophers, Robert McCarrison, Henry Shortt—to mention but a few of those whose painstaking labours have been instrumental in restoring health and happiness to countless millions of sufferers in all regions of the tropics.

In 1943, the Government of India ordered a review of the whole medical position of that sub-continent, with suggestions as to future improvements—in fact the details of a National Health Service to be worked out—but a Service on so vast a scale as to make that which now obtains in this country appear almost elementary. In India 100,000,000 persons suffer every year from malaria. There are, each year, 500,000 deaths from tuberculosis, and a further 2,500,000 active cases requiring treatment. Cholera, smallpox and plague have, indeed, been shorn of much of their former virulence, but the means of preventing the incidence of epidemics has not yet been found. Other diseases of the tropics—leprosy, filaria, hookworm and guineaworm—though they do not carry so high a mortality, saddle the country with innumerable chronic sufferers. To combat, adequately, these and the many other problems involved and to give a reasonably comprehensive health service for the whole of the population, would require a staff of 250,000 doctors and 750,000 nurses, in addition to a great army of associate workers. Whether that goal will ever be achieved only the future can show. The great Medical Service which served India so well during the last three centuries had well prepared the way but, when power was transferred in 1947, in spite of all that had been accomplished, it seemed that, in many ways, the journey had but just begun.

BOOKS RECEIVED FOR REVIEW

Bentley (A. O.), and Driver (J. E.). Textbook of pharmaceutical chemistry. 6th edit. Revised by J. E. Driver. pp. viii+751. London: Oxford University Press (Cumberlege). 55s. 0d. 1955.

Brain (Sir Russell). Diseases of the nervous system. 5th edit. pp. xviii+996. London: Oxford University Press (Cumberlege). 55s. 0d. 1955.

Cantarow (A.), and Trumper (M.). Clinical biochemistry. 5th edit. pp. xxxi+738. Philadelphia and London: Saunders. 63s. 0d. 1955.

Cowdry (E. V.). Cancer cells. pp. xvi+677. Philadelphia and London: Saunders. 112s. 0d. 1955.

Harris (G. W.). Neural control of the pituitary gland. (Monographs of the Physiological Society No. 3.) pp. x+298. London: Arnold. 30s. 0d. 1955.

Henry Ford Hospital. Symposium on cardiovascular surgery. Editor: Conrad R. Lam. pp. xxix+543. Philadelphia and London: Saunders. 89s. 0d. 1955.

Hetherington (W.). The compend: a compendium of ethical proprietaries used in medicine and pharmacy. pp. xxviii+676. Bristol: Wright. 32s. 6d. 1955.

Michels (N. A.). Blood supply and anatomy of the upper abdominal organs. pp. xiv+581. London: Pitman (Philadelphia: Lippincott). £8 0s. 0d. 1955.

Modell (W.). The relief of symptoms. pp. x+450. Philadelphia and London: Saunders. 56s. 0d. 1955.

Reed (S. C.). Counseling in medical genetics. pp. viii+268. Philadelphia and London: Saunders. 28s. 0d. 1955.

Rushmer (R. F.). Cardiac diagnosis. A physiologic approach. pp. viii+447. Philadelphia and London: Saunders. 80s. 6d. 1955.

Williams (R. H.), ed. Textbook of endocrinology. 2nd edit. pp. xii+776. Philadelphia and London: Saunders. 91s. 0d. 1955.

Williamson (P.). Office procedures. pp. ix+412. Philadelphia and London: Saunders. 87s. 6d. 1955.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Barton (B.). And now to live again. pp. 160. London: Quality Press. 1948.

Bateson (W.). Mendel's principles of heredity: a defence. pp. 212. Cambridge: Cambridge University Press. 1902.

Bayly (M. B.). The futility of experiments on animals. pp. 104. London: National Anti-Vivisection Society. 1954.

Benvenuti (M.). Introduzione alla neurologia clinica infantile. pp. 147. Pisa: "Omnia Medica." 1955.

Haeser (H.). Grundriss der Geschichte der Medizin. pp. 418. Jena: Gustav Fischer. 1884.

Harley (H. R. S.). Subphrenic abscess. pp. 176. Oxford: Blackwell. 35s. 0d. 1955.

Padlocks and girdles of chastity. pp. 115. New York: Golden Hind Press. 1932.

United States. War Department. Surgeon General's Office. Preventive medicine in World War II. Vol. 2: Environmental hygiene. (Medical Department, United States Army.) pp. 404. Washington: Surgeon General's Office. 1955.

Weber (F. Parkes). Rhymes, verses and epigrams. pp. 20. London. 1955.

Withering (W.). An arrangement of British plants. 6th edit. 4 vols. London: Scholey. 1818.

Section of Ophthalmology

President—R. C. DAVENPORT, F.R.C.S.

[*October* 13, 1955]

Uveitis

PRESIDENT'S ADDRESS

By R. C. DAVENPORT, F.R.C.S.

IN spite of the amount that has been written and spoken about uveitis in recent years, the ætiology of endogenous uveitis is still an unsolved problem and many features of the disease are obscure. I shall comment briefly on some clinical changes in the pattern of uveal inflammation and discuss the findings, both clinical and pathological, on the first 200 cases in the recently established Uveitis Clinic at the Institute of Ophthalmology. It was of special interest for me that from the clinical point of view A. G. Cross read a paper to this Section last year on Uveitis in Children (*Proceedings*, 1954, **47,** 971) and in the September 1955 issue of the *British Journal of Ophthalmology*, Smith and Ashton reviewed the ætiological aspect basing their paper on the laboratory findings of 200 cases they examined at the Institute. In reporting these findings I should like to take the opportunity of saying how much the work of both clinicians and pathologists serving the Uveitis Clinic is valued. Much of it is detailed and routine, and readily becomes tedious. I should like to thank them, and the Department of Illustration which has made slides for projection, for the very large contribution to the make-up of this Address. I knew that Smith and Ashton were engaged on this investigation last year but heard nothing of their findings until a few days before the paper appeared and it is perhaps of value that the pathological findings in their series can be compared with those of a similar number of cases from another series investigated in the same department. The main difference between the two groups, and Smith and Ashton referred to this aspect, is that their 200 had a preponderance of long-established uveitis cases attending clinics over the years where hitherto investigation and treatment had produced little result. The 200 cases which I have reviewed were referred in most instances from the first clinic visit. Many were comparatively mild, rapidly responding to treatment. Though perhaps not an entirely random selection they present another aspect of the picture complementary to that presented by Smith and Ashton.

In the edition of Parsons' which I used as my first textbook the traditional pattern of classification of uveal inflammation, viz. iritis, iridocyclitis and choroiditis, was followed, although it was stressed in the first paragraph of the appropriate chapter that "uveitis" (perhaps reasonably referred to as an uncouth term) was the accurate description for each and every case of such inflammation. I think the anatomical divisions were based in part at least on the clinical picture in which inflammation did seem more sharply confined to the several parts of the uvea than it does to-day. From the ætiological point of view we then knew the cause of a considerable proportion of the cases for, as quoted by Parsons, 25–30% of iritis and most cases of disseminated choroiditis were of syphilitic origin. I think a fair although crude picture of uveitis thirty or forty years ago would have been:

Iritis—recurrent in middle-aged and older males=gonorrhœal.
—recurrent in older people of both sexes="gouty" or "rheumatic".

Iridocyclitis—acute uniocular (usually single attack) in younger people=septic focus (e.g. teeth or tonsils).
—acute or subacute and often bilateral=syphilitic.
—chronic plastic, in middle-aged people, especially women=unknown ætiology, in younger people=tuberculous.

Choroiditis—disseminated, at any age=syphilitic, congenital or acquired.
—solitary, in young people=tuberculous (with less certainty about this ætiology as time went on).

In many instances the inflammation was severe and often blinding, and treatment was of limited value but at least the ophthalmologist knew the cause and derived human and professional satisfaction from this knowledge. The picture to-day is, of course, very different. I am afraid I am not able to quote figures of the comparative incidence of uveitis as seen at Moorfields or elsewhere. Records over the years do not give enough accuracy, but although the venereal element has for all practical purposes disappeared there is still plenty of inflammation of the uveal tract in every eye clinic. I propose to review the above classification against the clinical picture to-day.

The sharply defined clinical entity of gonorrhœal iritis has virtually disappeared but attacks abrupt in onset, sharp in course with rapid decline, affecting one eye or the other and recurrent over the years are quite frequently seen in young people, particularly in my experience in young women. The clinical course, the gelatinous exudate in the anterior chamber and the almost complete dispersal of all traces on subsidence of the attack, makes this a strikingly similar clinical picture to the other. One girl in my clinic had had recurrences in either eye at least yearly from the age of 15 to 25 and I have twice seen a hypopyon present with an attack in the right eye. Investigation has so far failed to find a cause and even now her vision is 6/5 in each eye.

A proof that the cases of iritis attributed to gonorrhœa were either infective or allergic from the gonococcus was not normally obtainable. It was quite customary for these clinical types to be treated with gonococcal vaccine but, on the acceptance of the fact that the ocular lesions stemmed from damage in the posterior urethra and vesicles, some held that a pyogenic infection of already damaged tissue was the cause of the iritis. Accordingly they used mixed staphylococcal and streptococcal vaccine in treatment and by implication the lesion was considered to be caused by focal infection. Is the response of the uvea here similar for various stimuli or is the stimulating agent the same in both cases?

In my experience recurrent iritis of old people—"gouty" or "rheumatic"—is far less frequently seen to-day and diabetic iritis has always been a comparative rarity. One patient in this series was described as having clinical gout over the years—a woman aged 33 with attacks since the age of 17. The history given was that her mother had had similar attacks of gout from her young adult life. The blood uric acid level was quite normal in this case and no clinical evidence of gout has been seen while she had been under hospital attention. The woman showed a typical bilateral anterior uveitis and the clinical picture was unlike the "gouty iritis" of the past. The E.S.R. in her case was consistently high but the antistreptolysin titre was in the low normal range.

The association of articular disease and anterior uveitis has been carefully studied and reported. For this series a routine X-ray of the sacro-iliac joints and vertebral column was not carried out but wherever there was any suspicion in the history or clinical picture radiography was used and in 6 cases ankylosing spondylitis was confirmed or found (4 men, 2 women). Their ages ranged from 28 to 63 (in this latter case the spondylitis was known to have been present for thirty years). As I am sure will be the general experience I have seen the association of severe anterior or even generalized uveitis with active spondylitis and equally the incidence and recurrence of attacks of anterior uveitis in men and women whose ankylosing spondylitis had been present many years and had been pronounced inactive over a long period prior to the onset of uveitis. The reverse can hold, for a previous history of, and the sequelæ of, anterior uveitis have been reported at the first examination of a case of ankylosing spondylitis.

Two elderly women in the series were cases of marked rheumatoid arthritis.

I have the impression, but I have not the figures to substantiate the statement, that destructive chronic uveitis, especially the type seen in middle-aged women and sometimes labelled involuntary but as far as I know of unknown ætiology, is becoming less and less commonly seen.

The typical clinical picture of disseminated choroiditis of the past, so often of syphilitic origin, seems to me to be replaced by a diffuse type of inflammation perhaps more commonly confined to the posterior pole than the periphery in which there is not infrequently seen retinal hæmorrhage and a generalized turgidity of the retinal venous system. The association of uveal inflammation, usually anterior, with vasculitis of one form or another in the retina seems to me to be increasingly frequently seen, for since I spoke of this association at the O.S.U.K. Congress in Newcastle in 1954 I have seen a number of such cases in my own clinic and more through the courtesy of my colleagues. Of the 200 cases examined at the Uveitis Clinic 24 (14 female, 10 male) showed sufficient change in the retinal vascular system to bring comment in the clinic report. In two or three patients the note was merely

that the retinal veins were turgid and these and one or two other cases where turgid veins and œdema of the nerve head were noted may all be explained by the anatomical proximity of uvea and retina. A number of cases, however, showed in varying degree actual vasculitis, exudates and hæmorrhages, and in one case arteritis with optic atrophy in one eye. Of the 24 cases only 2 were aged 40 or over and 18 were in the young adult range. In the large majority of this group no findings as to cause of either retinal or uveal inflammation could be established just as has always been the case with so-called Eales' disease. One of the cases of quite definite retinal vasculitis was the one case of sarcoidosis proved by biopsy. Two other were Mantoux negative at 1 : 100, and of the 24 cases 5 had a positive toxoplasma reading in the serum. Toxoplasmosis has been put forward in the United States as a cause of retinal vasculitis and it is perhaps of further interest that the case of uveitis associated with brucellosis reported by K. D. Foggitt in the *British Journal of Ophthalmology* last year showed retinal periphlebitis in one eye, perhaps also arteritis, as some degree of optic atrophy was present.

I am sure that during the last few years I have seen far fewer cases than formerly of sharply defined patches of acute solitary choroiditis in young adults. These inflammations with the gross haze in the vitreous settled in due course whatever treatment was employed. A fair proportion became reactivated in later years commonly adjoining the atrophic area of the first attack. The causation of these seems to me to have gone through the sequence of tuberculosis, focal infection and, more recently, toxoplasmosis. A firm proof of any of these causes has usually been lacking, and I think the sharply defined picture is much less frequently seen, the more diffuse posterior uveal inflammation taking the place of both this and, as I have suggested, the original disseminated choroiditis picture.

In reporting the pathological findings (Table I) I propose to set them out in the same way as did Smith and Ashton.

TABLE I.—CLASSIFICATION BY AGE, SEX, AND CLINICAL CATEGORY

Clinical category	*Sex*	*Age group* 0–9	10–19	20–29	30–39	40–49	50–59	60+	*Total*
Anterior	M	0	1	19	23	19	4	3	69
	F	1	8	15	14	12	13	7	70
Posterior	M	0	2	8	5	1	0	0	16
	F	1	6	4	2	3	0	0	16
Pan-uveitis	M	0	1	2	1	0	1	0	5
	F	0	0	0	0	1	0	1	2
Others	M	0	2	2	2	2	2	5	15
	F	0	0	0	1	3	0	3	7
		2	20	50	48	41	20	19	200
			Under 40=120.				Over 40=80.		

It will be seen that in total the females numbered 95 and the males 105. This is the reverse of the figures in Smith and Ashton's paper, and rather to my surprise and again against the findings of Smith and Ashton the male and female numbers are essentially the same in the 139 cases of anterior uveitis. There is no particular feature of the posterior uveitis cases to which I would draw attention but only 7 cases have I classed as pan-uveitis. The particular case which comes under this heading is perhaps somewhat arbitrarily decided, but Smith and Ashton's figure of 48 cases in this group is probably explained largely by the different type of patient with which they were dealing—the longstanding case of plastic uveal inflammation. The cases I have listed as "other" are a mixed lot in which I have included some sent to the Clinic for investigation although the presence of uveitis was not definite, 1 sympathetic ophthalmitis and possibly 1 other such case, the diabetics (4) and the heterochromic cyclitis and zoster cases. In age the numbers under 40 and over 40 are similar in the two groups (120–80) and although I only have memory and impression on which to base the statement I feel pretty sure that this 3 : 2 ratio for patients under 40 against those over this age would not have been the finding of 40 years ago.

Wassermann and Kahn reactions.—None of the 200 cases had a definitely positive Wassermann or Kahn reaction when examination was made this year. There was one doubtful positive result in a West Indian patient who did not return for a repeat test. 4 cases, however, had a positive case history of syphilis and of these 3 were known to have had a positive Wassermann finding at a previous date.

Gonococcal complement-fixation test.—In no case was this test positive but 3 men gave a history of gonorrhœa many years previously.

Mantoux test.—The issue of tuberculosis as a factor in the production of uveitis gets no clarification from this series and Smith and Ashton state that their survey failed to provide any laboratory criteria for the diagnosis of tuberculosis.

Of these 200 cases 24 were negative to a concentration of 0·002 P.P.D. (1 : 100 dilution). In both series of cases therefore the incidence of Mantoux-negative cases was just about that of the general population (12%). One girl in the present series was proved by gland biopsy to be a case of sarcoidosis but it is the only case so proved up to date and this survey offers little help in the assessment of the extent to which sarcoidosis can be the cause of uveitis. The case reported in the *British Medical Journal* (1955, ii, 593) by Ross of Carlisle makes very interesting reading. The bilateral anterior uveitis with nodules in the iris occurred in 1934 and regressed to complete settlement in spite of persisting hilar masses shown by X-ray; then occurred the subsequent involvement of the brain with death in 1954, and the demonstration at autopsy of cerebral, thoracic and liver foci of sarcoidosis.

TABLE II.—POSITIVE TOXOPLASMA RESULTS BY CLINICAL CATEGORY

		Dye test		*Complement-fixation test*	
Clinical category	*No.*	*Positive*	*Per cent*	*Positive*	*Per cent*
Anterior	139	50	36	11	8
Posterior	32	14	44	6	19
Pan-uveitis	7	1	—	1	—
Others	22	2	—	—	—

Toxoplasmosis (Table II).—The results in my series, although they show some degree of higher positive rate in the cases of posterior uveitis as against anterior, have not the same wide difference as in the results of Smith and Ashton's group where the figures were 67% against 39% by the dye test. I have found it very difficult to sort out any clinical pattern in the positive cases, for example, of the 6 cases in which ankylosing spondylitis was present 4 showed a positive toxoplasma result, 2 of them being strongly positive. I feel that in all this uncertainty as to the cause in any one case of uveitis the presence of ankylosing spondylitis is so satisfying from a clinical point of view that it seems a little hard that in 4 out of 6 cases the issue has to be queered by the serological reports.

Table III, which gives the age grouping of the positive cases, has one definite feature. Nearly 60% of uveitis patients over the age of 60 present a positive serological finding. The numbers are probably too small to be of account but the finding is of some interest.

TABLE III.—AGE GROUPS OF POSITIVE TOXOPLASMA

Age	1–19	20–39	40–59	60+
No.	7=32%	28=29%	21=34%	11=58%

Brucellosis.—1 patient in the posterior uveitis group agglutinated *Brucella abortus* to a titre of 1 : 256. There was no history or evidence of clinical infection in this case.

Anti-streptolysin assays.—The numbers, especially in the posterior uveitis group, are too small to give reliable figures on breakdown. Of the first 208 cases examined from the Clinic 53 showed a titre of over 100. This corresponds very closely to the rate 1 : 4 with a similar titre in the cases of anterior uveitis analysed by Smith and Ashton and is, I understand, a much higher rate than in the population in general.

Stress.—One of the workers in the Clinic has been going into the "stress" factor in the cases he examines. I imagine he wants many more cases on which to base conclusions but this possible element has not been overlooked.

In the problem of uveal inflammation why is it that so often the only area attacked in an otherwise very fit person is the scrap of uveal tissue? And how can we get at the causes? I feel sure that anterior uveitis is being seen more frequently in the younger age groups. When I was a student the aphorism was current "K.P. in a child means syphilis," but in 1954 Cross pointed out that the manifestations of syphilis in children are becoming rarities. Equally the severity seems to me to have diminished, largely, I think, because of decreased

incidence of chronic plastic uveitis aided by early diagnosis and modern treatment. This should mean fewer and fewer cases certified blind as a result of uveal inflammation. Mr. C. A. G. Cook kindly brought a patient to see me at Moorfields and has said I may quote the findings. I do this to show one pattern of case increasingly frequently seen and I will follow with the brief details of one case in the series. The two seem to illustrate so well the difficulty of ætiology.

In 1951 the child at the age of 7 gave the history of being struck in the left eye by a tennis ball and subsequently complained of affected vision. On examination at hospital the right eye gave 6/12 vision only, with an appearance of the optic disc described as pseudo-papillœdema, macular changes and tortuous retinal veins. The left eye showed much grosser changes with retinal hæmorrhages and exudates and vision of 6/60 only. All investigations as to the cause of this bilateral retinal lesion were negative. The right eye became more normal in appearance but the condition in the left altered little for four years at which time each eye developed an acute, though mild, generalized uveitis. There was still œdema of the discs and retinæ and some optic atrophy in the left eye suggested arteritis as well as involvement of the retinal veins. Every test has again been negative and there is no evidence of Still's disease or any other associated lesions.

Case No. 113 of my series was a female from my clinic who 14 years ago at the age of 27 first suffered from bilateral sclero-kerato-uveitis in each eye. Although there was no history of syphilis or sign of congenital origin the blood Wassermann was reported positive. There was, however, some doubt about the finding at that time. At any rate she was given a course of arsenical treatment and a full follow-up of mercury and iodide. Her Wassermann has been negative twice since the course of treatment. Now her Mantoux is positive 1/10,000 and her serum is positive to toxoplasma to 1 in 40 by the dye test. She has had gross dental sepsis, much "rheumatism" including severe lumbago, and her blood pressure at the age of 41 is 190/120. In spite of recurrent anterior uveitis her left eye still has 6/5 vision, though the right by reason of early complicated cataract has much lower acuity.

What has caused the uveitis in these two cases? The one has no trace of cause, the other a wide choice, for the patient seems to show the possibility of infection of various sorts, allergy from various causes and even "stress" and hypertension.

I think when we cannot get in the younger people even a clue as to the cause in such a high proportion of cases, and until we have a means of sorting out between multiple possible causes in one patient it seems almost hopeless to speculate even as between infection, whether by bacteria or a virus on the one hand, or tissue sensitivity on the other.

The veterinary surgeons have the same problem in the recurrent iridocyclitis of horses and you will remember the discussion in 1953 on this subject in conjunction with the Section of Comparative Medicine (*Proceedings*, 1954, **47**, 233). The disease in horses was first described in the Fourth Century A.D. and has, as in humans, been ascribed to all sorts of causes although I do not know that a stress element has been invoked. The general opinion now seems to be that there is no one cause but that the condition is one of allergic sensitivity which may be induced by a number of remote conditions in the animal. The epidemiology and the distribution of the diseases would seem to bear this out and give some support to the sensitivity causation of an inflammation in a small specialized pigmented tissue of the body. The Professor of Veterinary Science at the University of Belgrade, however, told me recently that in 80% of their affected horses the aqueous had a high titre to leptospirosis but that as in so many of our serological assays the picture was spoilt by the fact that in unaffected horses 30–40% showed a positive aqueous.

The classification of endogenous uveitis as between granulomatous and non-granulomatous, upon which Alan Woods has done so much detailed work, does not seem to me to have a clear clinical meaning, in the pattern of uveitis seen in our clinics to-day. At first sight the large majority of this group would be classified as non-granulomatous but while admitting the absence of streptococcal skin sensitivity tests it is hard to get any firm evidence that focal infection is the cause, and I for one could not frame a clinical "cause and effect" until more certain means of eliciting organism and site have been evolved. I wonder whether in the future, while all the time watching the clinical picture, we may not get more help from the study, especially perhaps the physiological study, of the uveal tract, than from a continued approach to the problem from the direction of the ways in which the uvea may be attacked.

REFERENCES

Cross, A. G. (1954) *Proc. R. Soc. Med.*, **47**, 971.
Smith, C. H., and Ashton, N. H. (1955) *Brit. J. Ophthal.*, **39**, 545.
Foggitt, K. D. (1954) *Brit. J. Ophthal.*, **38**, 273.

The Preliminary Results of the Treatment of Uveitis with Daraprim

By CHARLES SMITH, M.D., and E. S. PERKINS, F.R.C.S.

Dr. Charles Smith: *Experimental Studies.*

The treatment of all forms of toxoplasmosis is most unsatisfactory and until the reports by Eyles and Coleman (1953) and Summers (1953) the only agents known to have any effect were the sulphonamides. Eyles showed that 2:4-diamino-pyrimethamines were parasiticidal and that the best of these was probably Daraprim (5-[p-chlorphenyl]-2; 4-diamino-6-ethylpyrimidine). He concluded, however, that it was little more active than the sulphonamides and that they might well be used together as their actions were complementary.

Trevino *et al.* (1953) confirmed that the drug was toxoplasmacidal but suggested that there might be strain variation in the susceptibility to Daraprim and a further report by Ryan and others (1954), that the pyrimethamines were active in cases of human toxoplasmosis of a type which is usually unaffected by sulphonamides, suggested that it would be worth testing the sensitivity of an English strain of the parasite.

Methods.—The mice used were Swiss-Albino of 16–20 grams weight. Mice were infected intracerebrally and received 0·2 mg. Daraprim daily for five days. Daraprim was administered intraperitoneally as a suspension in saline. The results, shown in Table I, are

TABLE I.—TREATMENT OF MOUSE TOXOPLASMOSIS WITH DARAPRIM

	Number of survivors		
	3rd day	10th day	14th and up
Controls	18	2	0
Daraprim	18	16	14

(Mice infected intracerebrally. Daraprim 0·2 mg. daily for 5 days.)

most encouraging, and particularly so in view of the fact that treatment can be delayed until the animals are almost moribund and still one obtains a 50% cure rate; it is worthy of note that if Daraprim is administered so that toxic levels of the drug are reached, folic acid can be given as this appears to decrease the toxicity without decreasing the therapeutic efficiency, an effect first noted by Summers.

Experimental eye lesions.—One of the troubles of any tests of antitoxoplasmic drugs is that we have no good experimental model of the disease seen in the eye; the only animal toxoplasmic chorio-retinitis is seen in the late stage of the disease, in the golden hamster (Frenkel, 1955). The eye lesions seen in these animals are an incidental event in the fatal systemic disease. We have been working on producing a satisfactory eye lesion and fortunately we have recently discovered a strain (isolated from a fatal human case showing chorio-retinitis by Professor C. F. Barwell), which has the great advantage that it is not lethal to rabbits when introduced into the eye.

Treatment of these lesions.—Attempts to influence the course of the disease have been made with Daraprim. While the acute iridocyclitis that develops on the third to the fifth days is diminished by Daraprim, there appears to be no effect upon the choroidal lesion whether the drug is given systemically or sub-conjunctivally.

Disappointing results may be, in part, due to the relatively few experiments we have been able to perform, but more probably failure is due to:

(1) Failure of the drug to reach the lesion.

(2) An inadequate systemic dosage—too few experiments.

(3) Differences in the metabolism of the animals.

This last needs elaboration, but, briefly, it can be said that it is probable that pyrimethamines act as antagonists in the metabolism of folic acid probably preventing the conversion of folic acid to folinic acid. If this step was not essential in any animal's metabolism, it is possible that the drug would be inactive.

Unfortunately, since this paper was written the rabbits which received sub-conjunctival Daraprim have commenced to develop extensive cataractous changes in the lens, pointing to a penetration of the drug into the eye when given sub-conjunctivally. Fortunately, when the drug is given systemically no such cataractous change is seen.

While the results of our treatment of rabbit uveitis were equivocal, the success in the treatment of the mouse infections encouraged us to plan the clinical trial which Mr. Perkins is to describe.

REFERENCES

EYLES, D. E., and COLEMAN, N. (1953) *Antibiot. Chemother.*, **3**, 483.
FRENKEL, J. K. (1955) *Amer. J. Ophthal.*, **39**, 203.
RYAN, R. W., HART, W. M., CULLIGAN, J. J., GUNKEL, R. D., JACOBS, L., and COOK, M. K. (1954) *Trans. Amer. Acad. Ophthal. Oto-laryng.*, **58**, 867.
SUMMERS, W. A. (1953) *Amer. J. trop. Med. Hyg.*, **2**, 1037.
TREVINO, A., VARELA, G., and PALENCIA, L. (1953) *Rev. Inst. Salubr. Enferm. trop., Méx.*, **13**, 339.

Mr. E. S. Perkins: *Clinical Trials.*

The patients concerned in this trial have been, as far as possible, consecutive cases of active uveitis seen in the Uveitis Clinic at the Institute of Ophthalmology.

The patients all receive a full ophthalmological and general medical examination and a routine pathological examination which includes tests for toxoplasmosis. When patients are considered suitable for inclusion in the trial they are given one of two lots of tablets, according to a list of random numbers, and instructed to take one tablet a day for a month, after which their condition is reassessed under the following headings:

Visual acuity.

Aqueous or vitreous flare and cells.

Degree of injection.

Subjective response.

Degree of total objective change.

One group of tablets contains Daraprim 25 mg. and the other an inert substance, but the clinician dispensing the tablets and assessing progress does not know which contains the active substance. By this means the psychological effect of the treatment should be equal in all cases.

This report concerns the first 63 cases to complete a full month's trial and for whom pathological reports are complete. Of these cases 30 had an anterior uveitis, 20 a posterior uveitis and 13 a generalized uveitis. It will obviously be necessary at a later date to analyse the results of each anatomical group, comparing toxoplasma-positive and -negative cases, treated and untreated, but if this is done with the present series of 63 cases the numbers in each group are so small as to have little significance. The site of the inflammation has therefore been ignored in the present analysis, and the cases divided into four groups: (1) All cases having a positive dye test titre of 1 : 4 or more who received Daraprim; (2) cases having a positive dye test but who received the inert tablets; (3) and (4) treated and untreated cases with negative dye tests.

The results in the four groups are shown in Table I.

TABLE I

Toxoplasmosis dye test	*Treatment*	*No. of cases*	*No. improved*	*No. not improved*	*% improved*
Positive	Daraprim	21	16	5	76%
Positive	Inert tablets	15	8	7	53%
Negative	Daraprim	15	7	8	47%
Negative	Inert tablets	12	7	5	58%

At first sight it would appear that the results in the first group, the only group in which a response to treatment was likely, are definitely better than those of any other group. However, the number of cases in each group is relatively small and if the figures are tested statistically the results are not so encouraging.

Using the χ^2 test, a comparison of the first group with any other single group gives results which could easily be accounted for by chance. If, however, the first group is compared

with all the other groups combined, the probability that the apparent improvement in the first group is due to chance alone lies between 5 and 10 in 100. While this degree of probability is not sufficient in itself to enable us to say that Daraprim is undoubtedly exerting an influence on the results of uveitis cases treated with it, it certainly does not exclude this possibility. Similarly it is not possible to argue from the results that as there has been an improvement in the toxoplasma-positive cases treated with Daraprim over those with a negative toxoplasma reaction then some of these cases are due to toxoplasmosis, but again this possibility is certainly not excluded by the results, and we feel that it is well worth while to continue the trial, although it may be necessary to modify the dose of drug given. Recent reports have suggested that Daraprim gives good results when given in higher doses; unfortunately it is not free from toxic effects, and in one case in this series treatment had to be stopped on account of a decreasing white cell count, and it seems likely that if higher doses are to be employed the patients will have to be admitted and very carefully controlled during their treatment.

The trial is continuing, but, in addition, all cases with a positive dye test are receiving a course of Daraprim if they have received inert tablets in the trial.

I should like to thank Messrs. Burroughs Wellcome & Co. for the supplies of Daraprim tablets for use in this trial.

Dr. Norman Ashton:

In the problem of uveitis we have arrived at a stage where the old ætiological concepts no longer appear applicable, either because they were always erroneous, or because, as the President suggests, the disease itself has changed. Many of the old ideas, therefore, are being abandoned, but there is so little new knowledge upon which to base a modern ætiological classification that to-day the subject is beset with confusion and uncertainty. There is an old Basuto proverb which seems remarkably applicable: "If a man does away with his traditional way of living and throws away his good customs, he had better first make certain that he has something of value to replace them."

The limited survey which Dr. Smith and I reported recently (*Brit. J. Ophthal.*, **39,** 545, 1955) appears to show that toxoplasmosis is almost certainly an important factor in adult uveitis, particularly in the posterior type, and our findings were in agreement with those of Wilder (*Arch. Ophthal., Chicago*, **48,** 127, 1952) and Woods *et al.* (*Trans. Amer. Acad. Ophthal. Oto-laryng.*, **58,** 172, 1954). In future studies, I believe we should continue to concentrate on this aspect both in investigation, particularly of unfixed fresh tissues, and in therapeutic trials. The exact role of hypersensitivity in uveitis is exceedingly difficult to define, but it is apparently of great importance, especially in relation to the streptococcus, as shown by anti-streptolysin assays carried out in America and in this country.

It has always seemed to me an intriguing problem as to why the uvea, a relatively minute area of vascular tissue presenting few unique histological features, should so peculiarly react in an apparently healthy body. There are, of course, many other examples of such vulnerability; an example would be the specific involvement of glomeruli in acute nephritis and, as in the study of this disease, the fluorescein-antibody conjugation technique of Coons as used by Hill and Cruickshank (*Brit. J. exp. Path.*, **34,** 27, 1953) may prove of value in research on the uvea.

For, although there may be no structural peculiarities, the uvea may well contain distinct cytoplasmic, membranous or stromal elements, which it may be possible to reveal by demonstrating their antigenic component with fluorescein-labelled antibody.

Section of Physical Medicine

President—J. SHULMAN, M.B., Ch.B.

[*October* 12, 1955]

DISCUSSION ON ANÆMIA IN RHEUMATOID ARTHRITIS

Dr. J. J. R. Duthie (Rheumatic Unit, Northern General Hospital, Edinburgh):

No completely satisfactory explanation for the presence of anæmia in rheumatoid arthritis has ever been given. Various theories have been discussed and investigated, but none has proved wholly satisfactory. To ascribe this condition to toxic depression of the marrow is merely to evade the issue. The anæmia in an uncomplicated case is characteristically normocytic and hypochromic. The M.C.V. is within normal limits in the majority of cases while the M.C.H.C. is usually below normal. Studies of the marrow have revealed impaired hæmoglobinization of normoblasts. Increase in plasma cells and eosinophils has been observed in a proportion of cases. These studies have not as yet provided any key to the fundamental cause of anæmia in rheumatoid disease.

It has been reported by Robinson (1943) and Dixon and others (1955) that the anæmia is due in part at least to an increase in plasma volume, although Jeffrey (1953*a*) did not consider that changes in plasma volume were significant.

Subnormal values for serum iron have been recorded in rheumatoid patients by many workers. Nilsson (1948) found that hypoferræmia was most marked in patients with severe anæmia and active arthritis. Jeffrey (1953*a*) correlated low levels of plasma iron and hypochromia, but found no increase in the total iron-binding capacity, such as is found in anæmia directly due to iron deficiency. Iron given by mouth is ineffective in the majority of cases, but a proportion of patients undoubtedly improve when iron is given by the intravenous route. This would suggest that absorption of iron from the gut is impaired, but here the evidence is conflicting. Jeffrey (1953*a*) found absorption to be impaired in a number of his cases, but we have failed to confirm this observation.

Another possible factor in the causation of anæmia in this disease might be a reduction in the life-span of the red blood cells. Little work has been done on this aspect, although a few workers have measured the survival of normal erythrocytes in patients with rheumatoid arthritis. Brown and others (1944) found survival to be normal in one patient with "severe disease". Mollison and Paterson (1949) reported reduced survival in two patients given cells incubated in serum containing Rh-blocking antibody. The same patients were subsequently transfused again with cells not treated in this manner. In one case rapid destruction was again observed. In two more recent reports (Freireich *et al.*, 1954; Bunim, 1954) an increased rate of destruction was found in patients with active disease.

In the Research Unit at the Northern General Hospital, Edinburgh, this problem has been studied during the last few years in the hope that elucidation of the cause of this very persistent objective symptom might shed some light on the underlying cause of the disease. A considerable amount of information has been acquired which may be of some interest, and which I propose to review fairly rapidly in the hope that others may be able to find some pattern which we have not as yet been able to observe.

Metabolism of iron.—In view of the response to intravenous iron occurring in a number of patients (Sinclair and Duthie, 1949, 1950; Ross, 1950; Jeffrey, 1952, 1953*a*, 1953*b*) it was considered worth while to investigate further the metabolism of iron in rheumatoid disease.

Measurements of serum iron values in 35 healthy males and 21 males with rheumatoid

arthritis, 35 healthy females and 46 female patients were carried out and the results were as follows:

	Mean serum iron	S.D.
35 healthy males ..	181 μg./100 ml.	±25
21 R.A. males.. ..	113 ,,	±30
35 healthy females ..	135 ,,	±21
46 R.A. females ..	100 ,,	±26

The difference between controls and patients is highly significant. The total iron-binding capacity in 42 patients fell within normal limits.

Iron absorption was measured in 8 normal controls and in 14 patients. The test dose was 1·2 grams ferrous sulphate. Serum iron was measured before its administration and at two, four and six hours afterwards. No evidence of impaired absorption in rheumatoid patients was found.

It was decided to measure the time taken to clear iron from the plasma following a single intravenous dose of 200 mg. of saccharated oxide of iron (S.O.I.). This was done in 7 normal controls and 17 patients with rheumatoid arthritis. In the rheumatoid patients all the administered iron had been cleared within twenty-four hours. In normal subjects clearance was not complete until seventy-two hours had elapsed. The difference could not be accounted for by greater excretion of iron in the urine in the rheumatoid patients.

Soon after these experiments a dextran-iron complex, suitable for intravenous injection, became available, and it was decided to investigate how it was handled in patients with rheumatoid arthritis as compared to normals. Both preparations are colloidal solutions but the dextran-iron preparation is much the more stable of the two. Clearance rates from the serum of this compound were measured in 10 controls and 14 patients with rheumatoid arthritis. The rate of clearance of dextran-iron was much slower in both groups and the mean rate of clearance showed no difference between rheumatoid patients and normal controls. This was in marked contrast to the results obtained when saccharated oxide of iron was given.

It had previously been noted that a transient impairment of liver function followed the injection of 200 mg. of S.O.I. in normals but not in patients with rheumatoid arthritis. The serum bilirubin was measured in 7 controls and 17 patients and showed a definite rise in normals, not seen in patients. Similar experiments were carried out in 9 controls and 7 patients following the same dose of the dextran-iron preparation. No significant rise was noted in either the normals or the rheumatoids.

These experiments indicate that the two preparations of iron are handled in a significantly different manner by patients with rheumatoid arthritis. It is not clear at present whether this difference is due to the greater stability of the dextran-iron preparation, but it is hoped that further experiments will clarify this point.

Experiments were designed to observe the effect of ACTH on the rate of clearance of S.O.I. in rheumatoid patients. It was found that there was a distinct slowing up of iron clearance during the administration of this hormone, but following its withdrawal the clearance rate became as rapid as before. The results of these experiments indicate that suppression of the signs of inflammation by the administration of ACTH is accompanied by a return to a more normal rate of clearance of S.O.I. from the plasma.

Marrow iron.—In view of the report by Hutchison (1953) that the presence or absence of stainable iron in the marrow was a sensitive index of the need for iron, it was decided to apply his technique to marrow from rheumatoid patients. This was done in 49 cases, 20 males and 29 females. As an additional check on the technique, a method was devised for the chemical estimation of iron in comparable samples of marrow from the same sternal aspiration. There was agreement between the two methods. In 4 males and 11 females stainable iron was absent from the marrow. In none of these patients was there evidence of failure of absorption of iron or chronic blood loss. 7 of the 11 females had passed the menopause. In the majority of cases there was no correlation between the serum iron levels, the blood picture and the presence or absence of stainable iron in the marrow, although the group without iron in the marrow had a somewhat lower mean value for plasma iron and were a little more anæmic. The differences were not statistically significant. In one case stainable iron was absent from the marrow when the plasma iron value was 144 μg./100 ml. In another iron was present when the plasma iron was 39 μg./100 ml. It would appear, therefore, that in rheumatoid arthritis the presence or absence of stainable iron in the marrow provides no indication of the need of the blood-forming organs for iron.

The cytology of the marrow was studied in detail in 60 cases. A relative increase in normoblasts was seen in 19 cases. No defect in maturation or hæmoglobinization of the red cell series was recognized. An increase in plasma cells was observed in 21 cases and some increase in eosinophils in 5 cases.

In view of the unpredictability on any grounds of the likely effect of intravenous iron when a total of 1 gram was given, it was decided to increase the dose to 5 grams in the individual patient. It was felt justifiable to use these larger doses in view of the experimental evidence of Nissim and Robson (1949) and Nissim (1953) that very much larger amounts, weight for weight, could be given to animals. 9 of these patients have now been followed for three months. 4 others have completed their course but have not as yet been followed for three months and are not considered. In no instance have any immediate or late untoward effects appeared. One month after the end of the course all patients had shown improvement in the blood picture, the E.S.R. had fallen substantially and plasma iron had risen. There had been some improvement in functional status and a reduction in disease activity. These results were, on the whole, reasonably well maintained at three months, although the plasma iron had fallen somewhat and the E.S.R. had risen a little. The study of larger numbers of patients over a longer period will be necessary before any definite conclusions as to the value of these larger amounts of iron can be reached. Certainly no evidence of harmful effects has appeared up to the present.

Mention has been made of the possibility that reduced survival of the erythrocytes may contribute to the appearance of anæmia in rheumatoid disease. The survival time of normal erythrocytes was measured in 18 patients with rheumatoid arthritis and in 2 controls. The initial loss of red cells was abnormally rapid in all patients. The mean survival in days was calculated in accordance with the formulæ evolved by Brown *et al.* (1944). In their study the survival in 6 cases of idiopathic hypochromic anæmia ranged from 38·2 to 53·9 days with a mean of 44·8. In this series the average of the individual means was 17·6 days with a standard deviation of 4·88. There was no clear relationship between the rate of destruction and the initial degree of anæmia, nor did the number of red cells transfused appear to influence the subsequent rate of destruction.

It appears unlikely that patients with rheumatoid arthritis destroy their own cells at this rate, as no evidence of hæmolysis was found in these patients. 7 patients were given two transfusions, 1 from a healthy and 1 from a rheumatoid donor. In all 7 patients subjected to this procedure the initial destruction of healthy cells was more rapid than was the case when cells from rheumatoid donors were given, although the latter curves did not show strictly linear decay. The average of the mean survival times following transfusion of healthy cells was 16·9 days in contrast to that following the transfusion of rheumatoid cells which was 31·9 days. This difference is highly significant.

Two patients were given suppressive doses of ACTH before and following a second transfusion from healthy donors. There was no material alteration in the rates of elimination of donated cells although complete suppression of clinical signs of activity was attained in both cases.

In 2 patients a second transfusion was given following hæmatological improvement brought about by the administration of 2 grams of intravenous iron. In neither case was there any prolongation of survival following the second transfusion.

These results suggest that increased cell destruction may be one factor in the causation of anæmia, but it is certainly not the whole story, as evidenced by persistent hypochromia of the red cells. The reason for the more prolonged survival of cells from rheumatoid donors in recipients with the same disease remains to be found. Detailed studies of red cells from rheumatoid patients have not as yet provided an answer.

The apparent abnormality of iron metabolism does not appear to be directly or wholly concerned with the occurrence of anæmia, although in view of the response to large doses of intravenous iron there is obviously some relationship the nature of which is not yet clear.

The problem is one of great complexity, but it seems well worth while continuing the study. Perhaps the views of the other participants in this discussion will indicate the direction of future work.

REFERENCES

Brown, G. M., Hayward, O. C., Powell, E. O., and Witts, L. J. (1944) *J. Path. Bact.*, **56**, 81.
Bunim, J. J. (1954) *Ann. rheum. Dis.*, **13**, 365.
Dixon, A. St. J., Ramcharan, S., and Ropes, M. W. (1955) *Ann. rheum. Dis.*, **14**, 51.
Freireich, E. J., Ross, J. F., Bayles, T. B., Emerson, O. P., and Finch, S. C. (1954) *Ann. rheum. Dis.*, **13**, 365.
Hutchison, H. E. (1953) *Blood*, **8**, 236.

JEFFREY, M. R. (1952) *Ann. rheum. Dis.*, **11**, 162.
—— (1953*a*) *Blood*, **8**, 502.
—— (1953*b*) *Brit. med. J.*, **2**, 912.
MOLLISON, P. L., and PATERSON, J. C. S. (1949) *J. clin. Path.*, **2**, 109.
NILSSON, F. (1948) *Acta med. scand.*, Suppl. 210, p. 124.
NISSIM, J. A. (1953) *J. Path. Bact.*, **66**, 185.
——, and ROBSON, J. M. (1949) *Lancet*, i, 686.
ROBINSON, G. L. (1943) *Ann. rheum. Dis.*, **3**, 207.
ROSS, D. N. (1950) *Ann. rheum. Dis.*, **9**, 358.
SINCLAIR, R. J. G., and DUTHIE, J. J. R. (1949) *Lancet*, ii, 646.
——, —— (1950) *Brit. med. J.*, ii, 1257.

Dr. A. St.John Dixon (Rheumatism Research Clinic, University of Manchester):

In the course of some studies at the Massachusetts General Hospital on the fate of intravenously injected dyes in rheumatoid arthritis, we made a comparison of the Evans blue dye method of measuring blood volume with the radioactive sodium chromate red-cell tagging method, which does not depend upon a dye. The methods were applied simultaneously in ten women with typical, moderately active, uncomplicated peripheral rheumatoid arthritis of at least five years' duration, who were being treated in hospital with bed rest and symptomatic doses of aspirin. Ten normal women, matched as closely as possible for age, drawn from the hospital staff or from patients admitted for conditions unlikely to affect their blood, served as controls. It was found that the Evans blue method always gave a higher value for blood volume than did the red-cell tagging method, but that the ratio of the results of the two methods was the same in the patients as in the controls. The Evans blue method for measuring blood volume seems, therefore, as reliable in rheumatoid arthritis as in normal subjects.

We compared the actual figures for blood volume of patients and controls in an attempt to answer the question "Is the blood volume in rheumatoid arthritis normal?" There are, however, difficulties in making this comparison which may affect the answer obtained. Our patients, as a group, were less heavy than the controls. Since blood volume per kilogram decreases as weight increases, body weight is an unsuitable standard of reference. Surface area is no better, since its calculation depends on measurements of height which are impossible to do accurately when flexion contractions are present. The method finally chosen was a statistical one based on the co-variance of body weight and blood volume. There was no difference between the effect of weight on blood volume in the weight range of the patients and in the weight range of the controls. It was therefore possible to make a statistical adjustment of the mean blood volumes and to compare the result of the two groups as if they had the same mean weight. This was done for red cell mass, plasma volume and total blood volume, and it was found that the patients, who were more anæmic than the controls (mean hæmatocrits 36% and 42% respectively), had a significant 20% increase in plasma volume and a 9% increase in total blood volume. A 7% decrease in red cell mass failed to reach significant levels. In these patients, therefore, it seemed that the main cause of their apparent anæmia was in fact a hydræmia, and that there was little if any actual loss of red cells.

One additional piece of evidence was provided by a man with rheumatoid spondylitis with peripheral joint involvement, who had been maintained in relative remission with the aid of cortisone acetate for three years. His cortisone treatment was abruptly stopped, and signs of arthritis promptly recurred. With this he developed anæmia, his hæmoglobin level previously having been normal. Blood volume measurements were done by both methods before and after stopping treatment and suggested that this anæmia was almost entirely the result of expansion of the plasma volume.

Clearly, expansion of the plasma volume will not be the only cause of anæmia in rheumatoid arthritis, but it seems likely that it is one of the factors operating, but this particular factor would not be peculiar to R.A.

Comment.—I doubt if the non-linearity in the effect of body weight on blood volume that was found in Gibson and Evans' series of normal women above a certain weight can explain the difference between Dr. Jeffrey's results and ours in patients with rheumatoid arthritis. We did not find this non-linearity and, moreover, results in normal subjects do not take into account the factor of loss of weight. Dr. Jeffrey's patients had, as a group, the same body weight and surface area as his controls. This must mean either that his patients had not lost weight, or had lost both weight and height in proportion, which seems more likely, but if so this would make the patients and controls not as precisely comparable as at first sight appears. I think this question of standards of reference is making numerical

comparisons of this kind very difficult, and that the most likely explanation of our differences is the variation that can occur by chance between small samples of the rheumatoid population.

Since the improvement in the anæmia of rheumatoid arthritis which may follow administration of parenteral iron is not related to any demonstrable shortage of this element I would like to suggest that what is happening is that, in some way, iron therapy provokes a remission of the disease, and as the patient gets better his anæmia improves.

Dr. M. R. Jeffrey (Royal National Hospital, Bath) [Summary]:

It is clear that there is more than one cause for this anæmia. We find iron deficiency the most important but reduction in red cell formation and survival and possibly other factors may contribute. The anæmia is typically hypochromic and at times microcytic. Overt evidence of hæmolysis is absent. Marrow smears or cultures may suggest erythroid hypoplasia and in such cases the anæmia is usually refractory.

Iron deficiency.—The serum iron concentration is nearly always low. Total iron-binding capacity may be raised, indicating iron deficiency, normal or slightly low. After abolition of iron deficiency, the average value is probably a little low but this does not explain the observed abnormalities in iron metabolism. Free erythrocyte porphyrin may be raised and falls to normal after iron therapy. Marrow iron stores are usually reduced or absent.

This iron deficiency can occur without external blood loss. It is commonest in women, who often have scanty iron reserves even in health. In such people, a small regular diversion of iron away from erythrogenesis could easily produce iron deficiency anæmia. Several observations suggest such a diversion. After an oral dose of iron, normal absorption may occur despite a very small rise of plasma iron concentration (Jeffrey *et al.*, 1955). Presumably this is due to rapid removal from the plasma, which was observed by Nilsson (1948) after giving small amounts of inorganic iron intravenously. Elmlinger *et al.* (1953) using tracer doses of ^{59}Fe found a high turnover rate of plasma iron in rheumatoid disease; external counting showed that the liver accumulated more and the marrow less than normal of the injected dose. The converse situation may obtain in states of liver damage when the plasma iron tends to be high. Wintrobe's group (Greenberg *et al.*, 1947) found that, after an intravenous dose of inorganic iron, the liver and spleen accumulated much more in animals with experimental inflammation than in the controls. Thus it appears that some diversion of iron into the liver and spleen does occur in inflammatory states.

Hæmodilution.—Some describe a primary increase in plasma volume, causing anæmia by dilution of the red cell mass. We are investigating the blood volumes of a group of rheumatoid subjects and of some hæmatologically normal controls, matched by weight, age and surface area, using the Evans blue-hæmatocrit technique of Gregersen (1944). Provisional results are summarized in Table I, in which mean volumes per unit of body weight are shown, with the statistical significance of differences between appropriate groups.

TABLE I.—BLOOD, PLASMA AND CELL VOLUMES RELATED TO BODY WEIGHT

	Men			Women			
	Control	Rheumatoid	P	Control	Rheumatoid	P	Rheumatoid (weighted)*
No. of cases	20	35		22	53		
Plasma ..	47·9	51·1	0·2	48·7	53·4	0·05	51·2
Cells ..	32·3	24·7	<0·01	26·2	22·4	<0·01	21·8
Blood ..	80·2	75·8	0·2	74·9	75·8	—	73 0

*See text.

Volumes are expressed as ml./kg.

A highly significant reduction in red cell mass is seen in both sexes. In the men, some increase in plasma and decrease in blood volumes are present but might be fortuitous. In the women there is a significant increase of plasma which balances the reduction in cell volume. The group of rheumatoid women, however, contains relatively more lightweight subjects than the controls. If this unequal distribution is eliminated by calculating weighted means, the figures of the final column are obtained and the same pattern of volume changes is evident in both sexes.

Analysis of the relations of blood and plasma volumes with body weight shows that in neither sex do the total volumes increase in direct proportion to the weight; thus the volumes per unit weight fall as weight increases. In the women, both patients and

controls, volumes are more closely related to weight, and the decrease in volume per unit weight as weight rises is considerably greater than in the men. Total cell volumes are not materially related to weight. These results emphasize the importance of trying to secure groups with similar weight distribution and of considering the weighted mean values in our female groups, whose distributions were unequal.

Gibson *et al.* (1939) studied the volume changes in several types of anæmia and found a common pattern. Prominent was a regular reduction in red cell mass, in proportion to the degree of anæmia; plasma volume might be increased but usually to a lesser extent than the red cell reduction so that the total blood volume tended to be low. Allowing for the inequalities of weight in the women, our patients exhibit exactly the same pattern of changes.

If hæmodilution were a cause of this anæmia, it should be most evident in patients with very active disease or with iron-refractory anæmia. Our figures, however, exhibit no relation between volumes and sedimentation rate and there is no tendency for the iron-refractory patients to show exalted plasma volumes. We conclude that the presence of anæmia and lighter body weight account for the apparent increase of plasma in rheumatoid disease and that the hypothesis of hydræmia is unnecessary.

Therapy.—We give parenteral iron when distinct hypochromic anæmia is present (Hb below 90% in men or 80% in women). In round figures, the hæmoglobin reaches the normal range in half the patients, rises more than 10% in a quarter and alters little in the others. The effectiveness and toxicity of intravenous and intramuscular iron seem much the same but because the latter is so easily given, a long-term danger must be recognized. The body has no means of regulating its iron content by excretion and injected iron is therefore cumulative. Hæmochromatosis from repeated blood transfusions is now being seen; our younger patients may be in danger of developing it in thirty years' time from over-zealous intramuscular iron therapy. Parenteral iron should only be given when the laboratory has demonstrated hypochromic anæmia and the patient's age and previous treatment have been considered.

We have used cobalt only in one case of refractory normocytic, normochromic anæmia: her hæmoglobin rose from 70% to 90% during two months' treatment. Further information is needed about the action and possible uses of this potentially toxic substance.

REFERENCES

Elmlinger, P. J., Huff, R. L., Tobias, C. A., and Lawrence, J. H. (1953) *Acta hæmat.*, **9**, 73.

Gibson, J. G., Harris, A. W., and Swigert, V. W. (1939) *J. clin. Invest.*, **18**, 621.

Greenberg, G. R., Ashenbrucker, H., Lauritsen, M., Worth, W., Humphreys, S. R., and Wintrobe, M. M. (1947) *J. clin. Invest.*, **26**, 121.

Gregersen, M. I. (1944) *J. Lab. clin. Med.*, **29**, 1266.

Jeffrey, M. R., Freundlich, H. F., Jackson, E. B., and Watson, D. (1955) *Clin. Sci.*, **14**, 395.

Nilsson, F. (1948) *Acta med. scand.*, Suppl. 210, p. 140.

Section of Pædiatrics

President—J. VERNON BRAITHWAITE, M.D., F.R.C.P

[*October* 28, 1955]

Some Problems Connected with Enuresis

PRESIDENT'S ADDRESS

By J. VERNON BRAITHWAITE, M.D., F.R.C.P.

ENURESIS presents many problems. It is such a common condition and so often we can do so little about it. Of 500 unselected children between the ages of 4 and 14 attending outpatient clinics in Leicester, no fewer than 109, or 22%, were or had been enuretic. It is seldom associated with serious organic disease, and were it not for its social inconvenience and for the shattering effect it sometimes has on the happiness of the patient and of his parents, it might well be considered a normal condition. But as it may blight the lives of those who suffer from it, we must do our utmost to cure it. We might reasonably expect that this would be a relatively simple matter, but of the 273 enuretic children on whose cases this paper is based, only 164 have been cured, 86 have improved, and 23 have remained quite untouched by any treatment.

I cannot hope to deal with all the problems of this baffling condition in one short paper, but can only pick out some of those of causation and some of those of management.

Firstly, is enuresis primarily a psychological illness? Usually no organic lesion can be discovered, the patients are often nervous and immature in outlook, and emotional strain often makes it worse.

However, if it is a neurosis it differs from all others in being nearly always congenital (87% of my patients had never attained control), and even among acquired cases psychological treatment frequently fails. 31% of my cases appear to be psychologically normal. The rest showed various abnormalities, but all these were probably the result rather than the cause of their enuresis, and they were usually not serious, although one very intelligent little boy of 7 told me, when asked about his friends, "No, I haven't any friends; you see, I wet myself". The child does not gain anything by wetting himself—he loses. He loses not only some of his parents' affection and his friends, but his personal comfort. It may possibly be regarded as a symptom of regression but regression is very rare and other symptoms never met with in enuresis would surely be present. I think that it would be justifiable to say that congenital enuresis is not primarily a psychological condition, and that physical causes must be sought for and treated.

In our search for abnormalities of structure or function, we are immediately confronted with a major difficulty—the impossibility of getting normal controls. I know that many authorities compare their results with what they call "normals", but they do not say who these normal children were or how they persuaded their parents to allow them to be submitted to these examinations.

A thorough clinical examination is essential in all cases of enuresis, especially of the urinary organs. Winsbury-White (1941) has reported that vulvitis is common in enuretic girls and 53 of the 98 girls in my cases showed this. But how many non-enuretic girls have vulvitis? I believe that a good many have, but it is difficult to be sure. Winsbury-White also found meatal stenosis and stricture frequently in boys with enuresis and in my 175 boys 10 had meatal stenosis and 3 had strictures (not all were examined for this)—but how many apparently

normal boys have these lesions? Similarly, Twistington Higgins (1944) has found urethro-trigonitis, and Ellison Nash (1947) has commented on the frequency of coronal adhesions.

Coronal adhesions constitute a subject in which we can get some controlled observations since their presence can be detected at an ordinary routine examination. At first I was impressed by the number of boys attending the enuresis clinic who showed them—49 of 111 uncircumcised boys, or 44%. This seems a high proportion, as most authorities state that these physiological adhesions should disappear in early childhood. But I thought that it would be worth while examining the first 100 boys in each year of age seen by me in my routine duties. The results surprised me. While 98% of the newly-born showed them, as was to be expected, no fewer than 56% of those between the ages of 4 and 13 years had prepuces still adherent to the glandes, few, if any, complained of symptoms, and 78% had never suffered from enuresis.

Here is a factor that has been blamed for enuresis, and can be compared with unselected controls. The result exonerates the adherent prepuce. How many other of the lesions confidently postulated as causing enuresis would similarly be disposed of if control observations were possible?

Phimosis is still considered to cause enuresis; controls are easily obtained. 5 of the 175 boys with enuresis, or 2·8%, had phimosis. Among the controls 2·9% showed this condition. It cannot therefore be blamed.

Circumcision.—At one time I thought that this operation predisposed to enuresis as 60 of the 175 enuretic boys were circumcised, that is 34·3%. Of the 500 controls 138, or 27·6% were circumcised, and this suggested a possible ætiological connexion. On submitting these figures to a statistician, however, I learned that they were not statistically significant.

Among the most recent and interesting anatomical investigations is the work of Fisher and Forsythe (1954) who, using micturating cystograms, found that 61 of 135 enuretics had abnormalities of the urinary tract. These were chiefly posterior urethral valves, neurogenic bladder disorders, and bladder-neck abnormalities. But, of course, no one knows how often these abnormalities occur in children who do not wet their beds.

It seems then that although structural lesions occur with some frequency in enuresis it is difficult to assess their significance.

Functional abnormalities in enuretic children.—Poulton (Poulton and Hindon, 1953) has found that relative nocturnal polyuria is common in enuretics, and I think that this is a factor in its production. At least it would produce nocturnal frequency. But I cannot help feeling that a normal child would wake when his bladder was full. And that brings me to the question of excessive depth of sleep. This was noticed nearly one hundred years ago by Trousseau (1870), and 185 of my 273 children slept very deeply, that is 68%. This again can be checked by controls, and among 500 unselected non-enuretic children only 113 or 23% were said by their parents to be difficult to wake. This confirms the widely held opinion that hypersomnia is frequently a major factor in the production of nocturnal urinary incontinence.

There are two other common related symptoms, frequency and precipitancy: 192 of my patients passed urine once an hour or more, that is 70%. 142, or 52%, were said to have marked urgency. This was so marked in 81 of them that it was impossible for the patient to control the bladder by day. 20 of these diurnal enuretics were unconscious of the act of micturition—the others felt micturition proceeding, but were quite unable to stop it.

These symptoms suggest a severe disturbance of the neuromuscular control of the bladder and this should be confirmed by cystometry. But here again we run into the same difficulty as with other urinary investigations in children—at what volume of fluid and at what pressure does the normal child's bladder contract and produce the desire to micturate? Ellison Nash (1949) has supplied an answer. He says that the desire to micturate in a normal child occurs when between 100 and 200 ml. have been slowly introduced into the bladder. This desire is not accompanied by any rise of pressure which remains at or below 20 cm. of water. He found that more than half of the enuretics he examined showed uninhibited bladder contractions eventually resulting in micturition.

I have performed cystometry in 117 of my cases. The method I use is this: The child empties the bladder after the external parts have been cleaned and a number 5 soft rubber catheter lubricated with an anæsthetic jelly is passed. The amount of residual urine, if any, is noted. Sterile water is now slowly injected into the bladder from a 10 c.c. syringe. The volume at which the first desire to micturate is produced is noted and when this occurs the

syringe is replaced by a manometer of the type used for estimating the pressure of cerebrospinal fluid. The use of a cerebrospinal manometer is much easier and much simpler than the more usual Y-junction attached to a manometer. It is true that this gives a more accurate reading of the pressure at the moment the desire to micturate is produced, but I have found that the two methods give very similar readings.

The results I have obtained show that the bladders of my patients contract when very small amounts of fluid are injected. In only 4 did the volume when the first desire to micturate appeared exceed 100 ml. In 58 it was below 10 ml. I found also that the pressure was lower than I anticipated. It was estimated in 97 patients and was below 10 cm. water in 56.

There were occasional anomalous results. In 7 children desire to micturate was produced with a small volume and normal or low pressures, but when the pressure was raised subsequently by getting the patient to strain or by manual compression of the bladder, no desire resulted. The pressure so produced varied from 20 to 100 cm. of water. Such cases suggest that there is a deficiency in the path between the cerebral cortex and the bladder. Two others felt a desire to micturate when quite a small quantity of water was injected, but when an attempt was made to withdraw some, nothing could be sucked up into the syringe; and yet when the catheter was removed, the patient emptied the bladder voluntarily without difficulty. The only explanation I can think of is that there was spasm of the trigonal muscle. This might compress the catheter and interfere with withdrawal of the fluid, but would facilitate normal micturition.

Apart from these unusual occurrences, the majority of the patients showed frequency and urgency of micturition and a bladder which contracted with a very small volume of injected water at a low or normal pressure. Such a condition suggests that the detrusor muscle fails to relax normally—that there is, if you like, a detrusor achalasia. This is often associated with an abnormal depth of sleep, and the combination of these two factors results in the well-known picture of nocturnal enuresis. If the detrusor achalasia is severe enough, and especially if there are deficient nervous connexions between the bladder and the cerebral cortex, enuresis will occur during the day as well.

We can speculate freely on what conditions can produce this state of affairs (Fig. 1) such

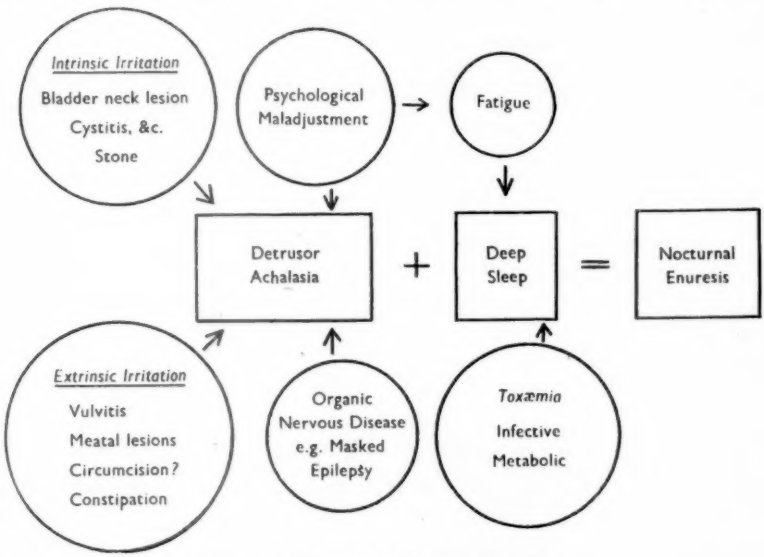


FIG. 1.—Detrusor achalasia and deep sleep.

as extrinsic irritation, e.g. vulvitis, meatal stenosis, and perhaps circumcision. Another common occurrence is incomplete emptying of the rectum. 133 of my patients had fæces present in the rectum, sometimes in large amounts, without feeling any desire to defæcate. But once more we cannot tell how often this occurs in non-enuretic children. I suspect that

it is quite frequent, as most children are expected to defæcate immediately after breakfast when they are afraid of being late for school. Intrinsic lesions such as urethrotrigonitis could easily produce bladder spasm. 28 of my boys had tenderness on pressure of the bladder base. I suppose that all of us have met with cases of acquired enuresis which clear up on curing a urinary infection. Such gross lesions as a vesical calculus may throw the detrusor into spasm. I have seen one boy who was cured by the removal of a large stone from his bladder. Lesions of the bladder neck such as have been described by Fisher and Forsythe (1954) may cause sustained hypertonus of the muscle.

Then there are lesions of the nervous system. Involuntary passage of urine is a classical accompaniment of epilepsy, and this condition must be eliminated as far as possible in all cases of enuresis. Turton and Spear (1953) found 22 examples of an epileptiform encephalogram in 100 enuretics. Probably cases of this type are the ones that respond to sedatives such as phenobarbitone. Diseases of the spinal cord must be eliminated, but it must be remembered that spina bifida occulta does not occur with any more frequency in enuretics than in normal people (Morrison, 1924). Among the causes of enuresis associated with the central nervous system must be mentioned emotional strain. Everyone is familiar with the effect of this on the bladder musculature, and it is undoubtedly a factor in some cases. I doubt, however, if it is a common exciting cause. It is certainly a result of urinary incontinence and may well help to perpetuate the symptom. It may also contribute to deep sleep by producing exhaustion and fatigue. Infective and metabolic toxæmia may also do this, and for this reason attention to the general health is of great importance in treatment.

I should like to conclude with a few words about treatment. If the symptom is caused by absence of detrusor relaxation it should be easily removed by the exhibition of antispasmodic drugs and by dealing with the cause if it can be discovered, and many patients can be cured by these means.

Scheme of treatment.—After the first interview and while the results of urinalysis or other investigations are awaited, I employ certain simple measures. These consist of thorough waking before wetting occurs (many parents "lift" their children and teach them to micturate in their sleep); reading or playing in bed for half an hour and then micturating, to get rid of the fluid that has been accumulated during the day in the lower extremities; getting the bowels well open at bedtime, when the tendency will be to prolong the session rather than to cut it short; and adopting a "start-stop-start" technique of micturition during the day, or micturating at set and progressively longer intervals; and the correction of any obvious psychological factors. The child is given a calendar on which dry nights are marked with coloured stars, a dry week being rewarded by a substantial gift. Some children are cured by these measures—33 of my 273. 28 others were very much improved—five dry nights or more a week—133 showed some improvement, and 79 were unaffected.

At the next interview, any infection of the urinary tract that has been discovered is dealt with. If the urine shows no infection, or if treatment of the infection does not stop the enuresis, drugs which inhibit contraction of the bladder are employed (Table I). I suppose

TABLE I.—TREATMENT BY DRUGS EMPLOYED SINGLY

Drug	No. of cases	Cured	Greatly improved	Improved	Unaffected
Belladonna	153	22	7	50	74
Pro-Banthine	33	5	2	11	15
Ephedrine and methyl ephedrine	110	13	6	34	57
Amphetamine	80	12	4	19	45
Phenobarbitone	21	4	2	10	5

that these drugs are the best remedies we have. Belladonna is the most time-honoured. It must be given in adequate doses—10 minims of the tincture twice a day and 20 minims at night to start with, increasing until signs of intolerance appear. 22 of 153 cases were cured by it, 7 greatly improved, 50 improved, but 74 were unaffected.

Other anti-cholinergic drugs such as Pro-Banthine bromide are a little more successful. Of 33 patients given Pro-Banthine in doses of 15–45 mg., 5 were cured, 2 greatly improved, 11 improved, and 15 were unaffected. Ephedrine and methyl ephedrine have much the same effect, although their action is a positive stimulation of the sympathetic rather than paralysis of its antagonists. Methyl ephedrine may be given in doses of 1–3 grains. Of 110 patients treated by it, 13 were cured, 6 greatly improved, 34 improved, and 57 unaffected.

Another point of attack on enuresis is deep sleep. For this amphetamine sulphate is the

obvious remedy and some enuretic children appear to be able to consume vast quantities of it without ill-effect. Some enuretics can take as much as 25 mg. at bed-time and still sleep soundly. I usually start enuretics with 5 mg. at bed-time and increase the dose until the patient wakes easily. When the enuresis occurs early in the morning, the slowly acting preparations of dextro-amphetamine ("spansules") are sometimes effective. Of 80 children treated with this type of drug 12 were cured, 4 greatly improved, 19 improved, and 45 unaffected. But with all these drugs used singly, only about half the number of patients are benefited.

Some very nervous children respond better to drugs of the barbiturate group. Usually they show on cystometry that they can tolerate relatively large amounts in their bladders but that the micturition reflexes are violent and uninhibited. Of 21 children given phenobarbitone, 4 were cured, 2 greatly improved, 10 improved, and 5 unaffected. Of course, some of these may be masked epileptics.

However, it is when we combine the various types of drug that we get the best results (Table II). The simultaneous exhibition of amphetamine to reduce the depth of sleep and

TABLE II.—TREATMENT BY COMBINED DRUGS

Drugs	No. of cases	Cured	Greatly improved	Improved	Unaffected
Amphetamine Belladonna	56	11	14	12	19
Amphetamine Pro-Banthine	13	10	—	1	2
Methyl ephedrine Belladonna	110	13	6	34	57

one of the anti-cholinergic drugs is frequently successful. 56 children were given amphetamine and belladonna; 11 of these were cured, 14 greatly improved, 12 improved and 19 were unaffected. Pro-Banthine and amphetamine have given the best results I have obtained so far, but the numbers are still too small to draw any safe conclusions. 13 patients have been treated with this and 10 of them were cured, and 1 improved. Sometimes belladonna and ephedrine together give gratifying results. But of 110 patients, only 13 were cured, 6 greatly improved, 34 improved, and 57 were unaffected.

Several other methods have been tried on a few patients with varying success (Table III).

TABLE III.—MISCELLANEOUS METHODS OF TREATMENT

Method	No. of cases	Cured	Greatly improved	Improved	Unaffected
Alarm bell	6	2	—	3	1
Mephenesin	11	2	—	3	6
Mephenesin and other drug	14	2	2	5	5
Hypnosis	33	5	11	5	12
Appendicectomy	1	1	—	—	—
Meatotomy	2	—	1	—	1
Dilatation of stricture	2	1	—	—	1
Cystoscopy	4	1	—	2	1
Distension of bladder	25	2	4	7	12

The alarm bell which rings when the sheets are wet is becoming very popular (Seiger, 1952). 2 of my patients have been cured by it, 3 have improved, and 1 was unaffected. But the apparatus is not mechnically perfect as yet. Mephenesin should be effective in children who have spasm of the trigonal muscle, but the condition is difficult to diagnose, and it may not exist. In 25 children in whom it was suspected, mephenesin, either alone or in combination with other drugs, apparently brought about a cure in 4, great improvement in 2, improvement in 8, and no change in 11. Hypnosis gives rather disappointing results: Of 33 patients, 5 were cured, 11 greatly improved, 5 improved, and 12 were unaffected.

Appendicectomy cured 1 patient. Other surgical measures employed are: meatotomy, 1 greatly improved and 1 unaffected; dilatation of stricture, 1 cured and 1 unaffected; and diagnostic cystoscopy, 1 greatly improved, 2 improved, and 1 unaffected. Possibly the improvement is the result of temporary dysuria.

C

I had hoped that distension of the bladder at weekly intervals would overcome the excessive detrusor tone, but the results have been disappointing. Of 25 children submitted to it, 2 were cured, 4 greatly improved, 7 improved, and 12 were unaffected. If it could be done more often, perhaps it would be more effective.

Summary

Enuresis has many causes and each case is an individual problem. It appears that incomplete relaxation of the detrusor is present in most cases, but what causes this is difficult to discover. When associated with deep sleep the combination of anti-cholinergic drugs and cortical stimulants seems to be the most effective treatment. But, with all the treatment at my command, I have only been able to cure 164 out of 273 patients, or about 60%. Most of the others have been improved to a greater or less degree, but 23 of them have been quite unaffected. What we are to do with this last type of case is perhaps the greatest problem of all.

REFERENCES

Fisher, O. D., and Forsythe, W. J. (1954) *Arch. Dis. Childh.*, **29**, 460.

Higgins, T. T. (1944) *Proc. R. Soc. Med.*, **37**, 344.

Morrison, W. K. (1924) *Brit. med. J.*, ii, 830.

Nash, D. F. E. (1947) *Practitioner*, **159**, 187.

—— (1949) *Ann. R. Coll. Surg. Engl.*, **5**, 318.

—— (1951) Urology of Childhood. London.

Poulton, E. M., and Hindon, E. (1953) *Arch. Dis. Childh.*, **28**, 392.

Seiger, H. W. (1952) *J. Pediat.*, **40**, 738.

Trousseau, A. (1870) Trousseau's Clinical Medicine. New Sydenham Society, London; **2**, 476.

Turton, E. C., and Spear, A. B. (1953) *Arch. Dis. Childh.*, **23**, 316.

Winsbury-White, H. P. (1941) *Brit. J. Urol.*, **13**, 149.

Proceedings of the Royal Society of Medicine

Vol. 49
39

Section of Odontology

President—Professor H. H. STONES, M.D., M.D.S., F.D.S. R.C.S.

[*October* 24, 1955]

Facial Pain: Review of Ætiological Factors

PRESIDENT'S ADDRESS

By H. H. STONES, M.D., M.D.S., F.D.S. R.C.S.

Professor of Dental Surgery and Director of Dental Education, University of Liverpool

Introduction.—There are special receptors for the transmission of pain and these are distinct from receptors concerned with the sensation of touch or thermal changes. These naked nerve terminals are found in the skin. subcutaneous tissues, mucosa, dental pulp, periodontal membrane, muscles, viscera and blood vessel walls.

The nerve fibres that transmit pain consist of myelinated and unmyelinated types. The myelinated fibres measure from 1 to 20 μ in diameter. These conduct impulses at varying speeds depending on their size, which ranges from 10 metres per second in the case of the smallest fibres to 100 metres per second in the largest. The unmyelinated fibres are small, being 1 μ or less in diameter, with a conduction speed of up to 2 metres per second. Thus smaller fibres, particularly the ummyelinated ones, conduct pain more slowly than the larger fibres.

The dental pulp of man, according to Brashear (1936) contains myelinated and unmyelinated nerve fibres, over 50% being less than 6 μ in diameter and the remainder 6–10 μ. These are pain-conducting fibres. Pfaffmann (1939) from functional studies in cats considered that they fall into the group with slow and variable conduction. Brookhart, Livingston and Haugen (1953), however, reported that in cats the afferent fibres of the tooth pulp consist of myelinated fibres ranging from 1–7 μ in diameter with an average of 3 μ. They terminate in relation to the odontoblasts losing the myelin sheath. From experimental work in which electrical stimuli were applied to the exposed dental pulp and recorded from peripheral segments of the trigeminal nerve and from the trigeminal complex in the medulla, they found no evidence of slowly conducted activity such as could be expected from impulses in small unmyelinated nerves. The transmission of stimuli through the dentine may be chiefly along Tomes' fibrils as there is reduced sensation when drilling secondary dentine which contains comparatively few or no fibrils.

The periodontal membrane contains nerve fibres of varying sizes (Brashear, 1936).

Painful impulses are transmitted along the nerve fibres to the posterior root ganglia of the afferent cranial nerves and spinal nerves, and thence via the sensory neurones to the cerebral cortex.

Pain may be caused by a noxious stimulus to the pain receptors. It may also arise if such a stimulus is applied to any part of a nerve trunk containing pain fibres and this also includes the central fibres and pathways; the pain will be referred to the area of distribution of the peripheral receptors of that nerve.

As there is sometimes confusion about the terms used in connexion with nervous lesions, it is necessary that they should be defined. Neuralgia is pain in or along the course of a nerve. The pain may be more or less continuous or it may be spasmodic as occurs in trigeminal tic. Neuritis is an inflammation of the nerve and, in the case of afferent nerve fibres, it may give rise to aching of varying intensity, but it frequently results in hypæsthesia, due to degenerative changes. Neurosis is a functional disorder occurring without any apparent material agent producing it, and without any inflammation or structural change. It gives rise to a great variety of symptoms and frequently makes diagnosis difficult.

The quality of pain varies and the usual division is into superficial and deep. Superficial pain such as arises from noxious stimuli affecting a cutaneous or mucosal surface has a pricking or, when prolonged, a burning sensation and is markedly localizable. Deep pain arises from noxious stimuli of deeper structures. It is diffuse, aching and localization is difficult. Cohen (1952) points out that all pain cannot be clearly divided into these two groups and that many mixed types occur as a lesion may involve structures giving rise to pain of both superficial and deep types.

Pathways

V and IX are the chief cranial nerves that carry painful impulses from the face and mouth to the brain. Mention will also be made of cranial nerves VII and X and of the great auricular nerve.

Painful impulses arising in connexion with deeper structures such as blood vessels are carried by sympathetic fibres and ganglia via the white rami communicantes to the posterior root ganglia.

Attention was drawn to the results of some recent work including that of Cook (1949) who considers that the long sphenopalatine nerve participates in the innervation of the maxillary central incisors.

The centre for the recognition of pain may well be the complex mass "prefrontal cortex-thalamus" (Wright, 1952). Strong and Elwyn (1953) state that there are probably a few cutaneous afferent fibres from cells in the facial ganglia which together with similar fibres from the vagus and possibly the glossopharyngeal nerves aid in the innervation of the external auditory meatus and skin of the back of the ear.

Classification of Facial Neuralgias

The various conditions that give rise to facial and oral pain will be considered under an ætiological classification as follows: Symptomatic neuralgia (excluding cranial and paracranial lesions); paroxysmal trigeminal neuralgia or tic douloureux; post-herpetic trigeminal neuralgia; glossopharyngeal neuralgia or tic; chronic neuralgia of the face and jaws; facial migrainous neuralgia; neuralgia due to cranial and paracranial lesions; causalgia; neuralgia of psychogenic origin.

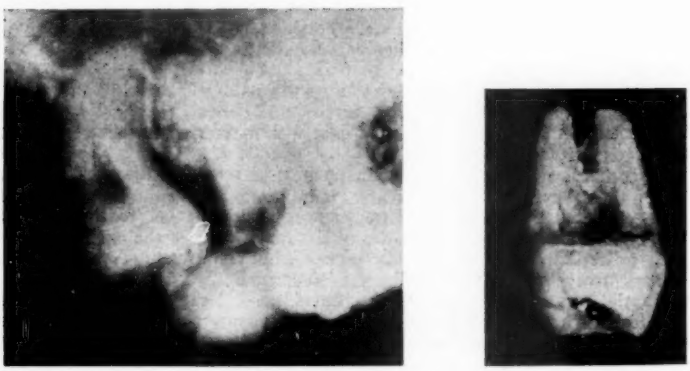
Symptomatic Neuralgia (Excluding Cranial and Paracranial Lesions)

Symptomatic or secondary facial neuralgia, excluding cranial and paracranial lesions, may be caused by the following conditions:

(1) Dental and Oral Causes

Pulpal conditions.—In acute closed pulpitis pain, which at first is of short duration and intermittent, is increased by thermal changes in the mouth. With total involvement of the pulp in the inflammatory process, the pain is extremely severe and of a persistent throbbing type, worse in the recumbent position. At this stage it is sometimes relieved by cold. In acute open pulpitis the pain is not so marked. In acute pulpitis the tooth is hypersensitive to the electric pulp tester. In chronic pulpitis pain is not a feature and more frequently the patient complains of a dull ache increased by heat. The tooth may be hyposensitive to the electric pulp tester.

As the pulp only possesses pain receptors, the patient may not be able to locate the involved tooth and it is not sensitive to percussion unless the inflammation has extended to the periodontal membrane. In pulpitis the pain may be referred to another division of the trigeminal nerve on the affected side (Fig. 1A, B). There also may be an associated area of skin tenderness.



A B

Fig. 1.—A, Maxillary left third molar impacted against second molar, the distal aspect of which had undergone resorption and caries with consequent pulpitis. History of bouts of neuralgia affecting the *mandibular* teeth and neck on affected side for previous seven months. Caries hardly detectable on clinical examination. B, Shows caries in extracted second molar. Female, aged 29.

Large metal fillings: A painful reaction may be produced by changes of temperature in an unlined metal filling, and in the case of adjacent dissimilar metal fillings, by galvanic action.

Pulp stones: These are of very frequent occurrence, and the incidence increases with age. They are usually associated with degenerative changes in the pulp and rarely give rise to pain. When such a symptom does occur, it is usually in young adults.

Periodontitis, periapical abscess and osteomyelitis.—In acute periodontitis there is a continuous ache and as the periodontal membrane possesses receptors for pain and touch the patient can locate the affected tooth which is sensitive to percussion. When pus is formed in acute abscess and also in acute osteomyelitis the ache is extremely severe while it is confined to the bone, but is eased when it perforates the bone. Again, in infected socket following tooth extraction, there is a continuous ache. In chronic infections the aching is not severe provided there is drainage of pus.

Impacted and unerupted teeth and odontomas.—The mandibular third molar is the most frequently impacted tooth. Pain may arise from inflammation as when pericoronitis or periodontitis supervenes. It may result from pressure on nerve fibres, or from resorption of the adjacent tooth and involvement of its pulp, in which case the pain may be referred to the teeth of the opposing jaw on the same side. Fig. 1A, B is an example of an impacted tooth which had given rise to pain.

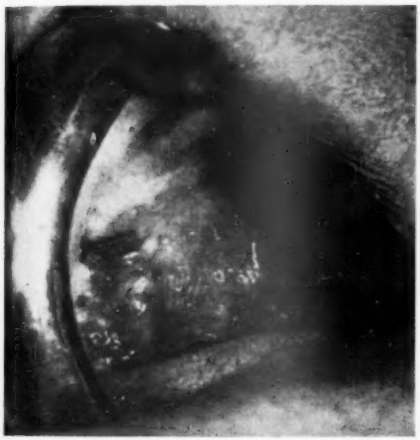


FIG. 2.—Squamous cell carcinoma of right side of soft palate extending to alveolar margin. Patient who is edentulous had worn dentures for twenty-two years. Tenderness of the affected region had been noticed for one year. Male, aged 64.

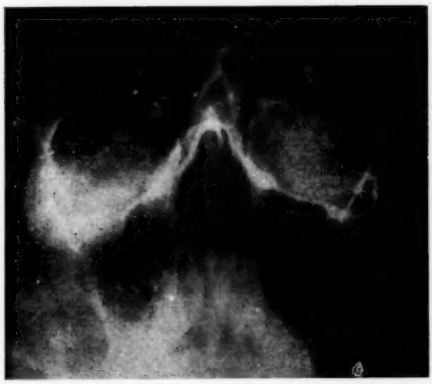


FIG. 3.—Maxillary sinusitis of right side. For about three months patient had complained of intermittent neuralgic pain of upper jaw and spreading to lower jaw of affected side. Male, aged 20.

Traumatic injuries of the jaws.—If the injury involves the bony channel of an afferent nerve, and this most frequently occurs in connexion with the inferior dental, it may give rise to neuralgia. More frequently, however, there is paræsthesia or hypæsthesia of the skin and mucosa supplied by its peripheral branches. This latter feature also predominates in severer injuries involving the trigeminal ganglion and in these cases there may be involvement of other cranial nerves (Jefferson and Schorstein, 1955).

Ulcers and stomatitis.—Ulcers may cause superficial pain; this is particularly marked in recurrent aphthæ and aphthous stomatitis. Fusospirochætal stomatitis may give rise to a continuous type of pain. Atrophic mucosal lesions often cause a burning sensation.

(2) TUMOURS OF THE JAWS

Compression symptoms may arise from tumours if there is encroachment on a nerve. Such pressure may result in neuralgia and paræsthesia or hypæsthesia to a varying degree (Fig. 2). In some cases, and this most frequently occurs with malignant tumours, severe pain and minimum sensory loss are first observed. In others, and this is when there is much destruction of nerve fibres, hypæsthesia is the most marked feature. Cysts of the jaws very rarely cause neuralgia unless complicated with an acute infection.

(3) Post-irradiation Causes

If necrosis and infection follow irradiation of a tumour about the jaws they may lead to a severe and constant neuralgia from involvement of nerve filaments.

(4) Chronic Displacement of Mandibular Condyle, Arthritis

After the extraction of teeth, if the correct vertical dimension of the jaws is not maintained when making dentures so that there is overclosure, the position of the head of the mandible in the articular fossa is altered. Normally the head should be centrally placed in the fossa both in the rest position and on closure. If, however, there is overclosure the posterior joint space is diminished. This abnormal positioning may lead to thinning of the tympanic plate and may affect the interarticular disc which also may be thinned. Bauer (1940), from histological studies, states that the disequilibrium may affect the cartilage layer of the subchondral bone which leads to progressive alterations in the surface of the disc, and that, gradually, osteoarthritis of the joint develops. Mandibular displacement may occur in occlusal abnormalities as from cusp interference.

There may be a click or cracking noise in the joint during movement, usually without pain. Costen (1934) drew attention to the overclosing producing a neuralgic syndrome in which there is headache about the vertex and occiput, ear symptoms of tinnitus and deafness, and glossodynia with a burning sensation in the tongue and throat. It is not proposed to consider the various postulates as to the mechanism of this hypothesis and particularly with regard to the effect on the auditory function; they have been reviewed elsewhere (Stones, 1954). Campbell (1955) who has examined over 500 cases states that the facial pain patterns vary enormously, and that the pain distribution usually defies rationalization though it is found to be associated with muscles. Relief is obtained in a certain number of cases by opening the bite and repositioning the jaws in the correct vertical and lateral relationship.

In view of this sequence it would be expected that the much more severe derangement of the joint following fracture-displacement or fracture-dislocation of the condyle treated without surgical intervention would be a frequent source of pain. This may occur in the early stages but MacGregor (1955) from a follow-up of a number of cases reports that chronic pain is very rare.

(5) Paranasal Sinus Lesions

In acute sinusitis pain is more often a feature than in chronic infection. Acute frontal sinusitis may cause severe pain which is chiefly located over the frontal region. Pain is not such a marked feature in infection of the other sinuses. In sphenoidal and ethmoidal sinusitis the aching, if present, is behind and between the eyes. In maxillary sinusitis the pain is usually most marked over the malar region (Fig. 3). The pain is held to be largely due to pressure in the sinuses as occurs if the ostia are occluded. McAuliffe, Goodell and Wolff (1943), however, found that a positive pressure within the maxillary sinus of 15–25 mm.Hg applied over quite a long period did not produce pain, and that it required a pressure of 200 mm.Hg to produce pain immediately. They consider that the state of inflammation and engorgement of the mucosa of the turbinates, ostia and superior nasal structures is the basis of most of the pain attributed to the paranasal sinuses. Sicher (1944) considers that the progressive expansion of the sinus in older people causes resorption of the walls of one or more of the channels containing the nerve filaments, thereby leaving the connective tissue that covers the nerve and the small accompanying blood and lymph channels in direct contact with the inflamed mucosa. The resultant type of pain then may resemble a pulpitis but stimulation of the maxillary teeth in that region will reveal that not one but a whole group are hypersensitive.

New growths and cysts in the sinuses may or may not cause pain. A tumour involving the posterior wall of the maxillary sinus may cause severe pain simulating a trigeminal neuralgia (Zamora, 1951).

(6) Elongated Styloid Process

Pain arising from an elongated styloid process has been described by Eagle (1937, 1948), Fritz (1940) and Douglas (1952), and from a fractured process by Douglas (1953). It is possible that the process either compresses sensory nerve endings of V, VII, and X cranial nerves, all of whose branches supply the involved area, or the perivascular nerve plexus of the external carotid artery. The usual symptoms are dysphagia, fullness or soreness of the throat, and sharp lancinating pains in the ear and lower jaw of the affected side. On digital pressure against the tonsillar fossa the hard elongated process can be palpated and the pain reproduced. This and the X-ray findings assist in the differential diagnosis from glossopharyngeal neuralgia.

Treatment consists in incising the mucous membrane over the area and removing the styloid process. In the case of the fractured styloid process relief of pain was obtained by immobilization of the jaws for three weeks.

(7) AFFECTIONS OF THE EAR

There is a multiple nerve supply to the ear, which receives twigs from the V, VII, IX and X cranial nerves. Hence noxious stimuli from parts remote from the ear may cause pain to be apparently situated in the vicinity of the ear. An example of this is the pain that sometimes occurs due to irritation of the third division of V nerve from pulpitis.

Conversely noxious stimuli arising in the ear may cause pain in any part of the front of the head, in the nasopharynx, larynx and back of head and neck (Wolff, 1948).

(8) AFFECTIONS OF THE EYE

In recurrent corneal ulceration and acute glaucoma pain is experienced chiefly in the eye, but it may spread over the area supplied by the ophthalmic nerve.

(9) CONTRACTURE OF FORAMINA

This may be the explanation of an obscure neuralgia. It may occur in certain osteodystrophies such as osteitis deformans, leontiasis cases and osteopetrosis (Fig. 4). Pain has

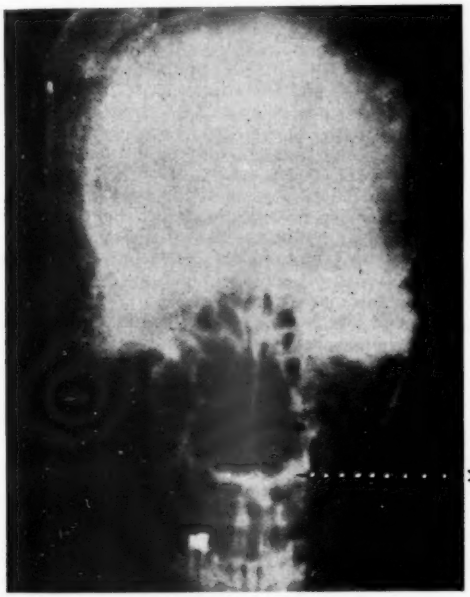


FIG. 4. — Osteitis deformans. Patient attended because of dull pain in left malar region. Note radiopaque area (X) in that situation and the mottled appearance of the skull. Patient was previously unaware that she was suffering from this osteodystrophy. Female, aged 47.

also been observed, though rarely, in the mental foramen region after tooth extraction where there has been excessive alveolar resorption.

(10) CORONARY THROMBOSIS

Reference was made in the anatomic description to the association between the descending branches of the trigeminal ganglion that form the spinal nucleus of V nerve and the top of the dorsal column of the grey matter of the spinal cord, and also to the distribution of the great auricular nerve. These factors explain why in coronary thrombosis the pain, which is located in the chest which is supplied by the upper spinal nerves, and often spreads to the arms and neck which are supplied by the cervical nerves, may occasionally extend to the lower jaw and teeth.

PAROXYSMAL TRIGEMINAL NEURALGIA OR TIC DOULOUREUX

Ætiology.—The cause of this spasmodic neuralgia, which usually occurs in middle or old age, is obscure. Harris (1950) for many years and Rowbotham (1954) consider that the pain is of peripheral origin as if it were of central origin neither peripheral nerve block nor neurectomy would give relief. The pain has been attributed to sclerosis of cells of the trigeminal ganglion, or to vascular changes, such as arteriosclerosis, vasospasm or vasodilatation of the blood vessels in the region.

Rowbotham (1954), however, who has operated on 176 cases in which the trigeminal pathways were approached extradurally via the middle fossa, states that although the middle meningeal artery varied in size, neither the artery itself nor its large branches were

found in such a position that they might beat against the second and third division of the nerve or against the ganglion. The dura was of varying thickness. Lengths of the third and second divisions, pieces of ganglion and lengths of the posterior root were examined histologically and of 15 specimens none was found to show any lesion.

Taarnhøj (1952) has obtained relief of pain without loss of sensation by the operation of decompression or cutting and freeing the sheath of the nerve root of V and the trigeminal ganglion. This may help to elucidate the ætiology of trigeminal tic.

Wyburn-Mason (1953) considers that a proportion of cases is due to a disturbance of the branches of the cervical plexus, especially of the great auricular nerve. His reason for this view is that he has used alcohol block or surgical section of the great auricular nerve in 56 cases of tic douloureux with marked relief of symptoms in about half the cases provided the tongue is not involved. It does not relieve pain in the tongue. A further follow-up report of the alleviated cases will be of much interest.

Clinical features.—Pain is the outstanding symptom. It is nearly always unilateral and usually affects either the second or third division of the trigeminal nerve. It may commence in one of them and in course of time involve both divisions. The first division is only rarely affected. The pain is characterized by its sudden onset and paroxysmal nature. In the early stages the pain is not so severe and the intervals between attacks may be quite lengthy, but as time goes on the pain becomes increasingly acute and the attacks more frequent. The pain is described as of a searing nature and occurs in attacks that last from a few seconds to a few minutes. A paroxysm may be started by a variety of minor causes in different patients, such as touching or stroking the affected side, draughts of cold air, cold water, or even undue movement of the jaw. Sometimes there is a "trigger zone" which, if touched, precipitates an attack. The lips and face are moved as little as possible, as the patient is afraid of an onset, and hence a rather mask-like expression is characteristic. During an attack motor symptoms occur in which, due to the anguish, there is spasmodic contraction of muscles of the jaw, face and eyelids. Vasomotor symptoms may be present as evidenced by redness over the area and distension of the veins. There is stimulation of the secretory nerves causing lacrimation, increased nasal secretion and salivation.

The ordeal and anguish gradually have an effect on an otherwise well patient. Frightened lest an attack occur, the appearance is that of great distress. The rationale for trigeminal interruption either by alcohol injection or differential retrogasserian root resection is to prevent what should be benign stimuli from touch or muscle movement from reaching the brain.

Post-herpetic Trigeminal Neuralgia

Ætiology.—Herpes facialis is due to a virus infection with an affinity for nerve cells and affects the trigeminal ganglion. There is fever and a unilateral eruption, often with pain along the affected nerve (Fig. 5). It most often attacks the ophthalmic nerve and involvement of other divisions is rare. The pain may only last for several weeks or become chronic.

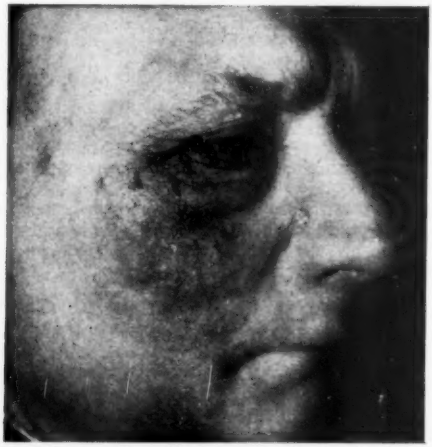


Fig. 5.—Herpes facialis. History of maxillary right canine having been extracted fourteen days previously and no pain or symptoms for first seven days. Onset was marked by a dull ache. There are unilateral herpetic lesions over the cutaneous distribution of the maxillary nerve and on oral aspect of upper lip. Male, aged 50.

Post-herpetic neuralgia usually occurs after 40 years of age. The precise disturbance that is responsible for the pain is unknown.

Clinical features.—It is characterized by a burning or boring deep pain which is always present, the severity varying at different times. In addition in some patients there is also a lancinating tic-like pain which is evoked by sensory stimulation of trigger zones as occurs in trigeminal tic. Sjöqvist (1938) reported that retrogasserian neurotomy has failed to relieve the pain and (1948) that trigeminal tractotomy failed to give relief in 2 cases.

Glossopharyngeal Neuralgia or Tic

Ætiology.—The cause of glossopharyngeal neuralgia or tic, which was described by Harris (1921), is unknown.

Clinical features.—The pain is spasmodic in character like trigeminal neuralgia, but differs in the area of involvement. Paroxysms of pain occur along the distribution of the nerve. It is nearly always unilateral. The areas affected are the side of the throat, base of the tongue, and back of the ear. It is usually initiated by taking a drink of cold water, by sneezing or coughing, and a "trigger zone" has sometimes been demonstrated in these sites. The pain usually only lasts for a second or two. Remissions are frequent and have been reported to last from several weeks to a few years. Diagnosis of glossopharyngeal neuralgia can be confirmed if relief is obtained by painting the tonsillar area with a cocaine solution (Coburn and Shofstall, 1941).

Cohen (1937) who has had 8 such cases points out that it must be differentiated from secondary glossopharyngeal neuralgia which is described later under cranial and paracranial lesions.

Chronic Neuralgia of the Face and Jaws

Ætiology.—There is a group of conditions, sometimes designated as atypical facial neuralgia and now considered to be of vascular origin, in which the pain during a bout is constant and does not necessarily follow the distribution of the V or IX cranial nerves.

The neuralgia described by Sluder (1918) which probably comes within this group, was originally thought to be due to irritation of the sphenopalatine ganglion as the pain was relieved by the application of a 2% solution of cocaine hydrochloride just behind the attachment of the middle concha but Behrman (1949) points out that any painful nasal condition can be relieved by this procedure. Wolff (1948) considers that this pain is due to vasodilatation of the third portion of the maxillary artery that supplies the area round the ganglion.

There is considerable evidence that deep pain can be produced by periodic vascular disturbances, particularly vasodilatation, and by traction or displacement of blood vessels.

Fay (1932) found that stimulation by faradic current about the bifurcation of the carotid artery is painful, and that the pain may be referred to various parts including the tongue, upper and lower jaws and orbital region, depending on the point stimulated. He considered that this type of pain probably finds its portal of entry to the brain through branches given off by the vagus nerve which associate themselves with the large cranial vessels and travel with the sympathetic branches to their field of distribution; and that fibres from the lower cervical and upper thoracic cord, by way of the carotid sheath, are important pathways for this type of pain. Glaser and Beerman (1938) and Campbell and Lloyd (1954) following an examination of 200 and of 40 cases respectively of atypical facial neuralgia found that usually the facial pain was associated with pain in the neck—tenderness of the superior cervical sympathetic ganglion—and often with pain in the shoulder, arm and eye, and stress the presence of vasomotor phenomena. Hardy, Wolff and Goodell (1940) state that aching pains in the muscles, bones and viscera are carried mainly in afferent sympathetic fibres presumably myelinated and non-myelinated and of varying size.

Clinical features.—The pain in this group is deep, diffuse and steady during an attack; the site of the pain and the frequency of attack vary in different cases. There may be vasomotor disturbances with flushing. There is no trigger zone. A number of patients are seen with symptoms which appear to come within this category. Treatment that has been tried includes vitamin B_{12} 1000 μg. daily for a fortnight followed by a maintenance dose of 100 μg. weekly, cervical sympathectomy, and section of the great auricular nerve.

Facial Migrainous Neuralgia

Ætiology.—Harris (1936) considers this entity is due to vasomotor disturbances of the blood vessels of the dura especially the middle meningeal artery, the pain being referred along the recurrent meningeal branches of the trigeminal nerve. Dott (1951) considers the cause to be a periodic relaxation and dilatation of the larger branches of the external carotid artery supplying some of the facial structures.

Clinical features.—It is characterized by unilateral pain in the temple, cheek, eye and jaw. Sometimes the superficial temporal artery can be seen to be dilated. It is accompanied by nausea but not vomiting. There is lacrimation and congestion of the eyeball. An attack works up to a crescendo in about ten minutes and may last for some hours. The attacks may be daily and occur for some weeks after which there may be a long remission before the next series.

Dott (1951) quotes Sir Charles Symonds as stating that the attacks can be controlled by intramuscular injection of ergotamine tartrate 0·25 mg. daily. The dose is omitted once a week to see if the bouts have subsided. Trigeminal ganglion alcohol injection or, if the pain is confined to one area of the face, fractional retro-gasserian root resection, alleviates the condition.

Neuralgia Due to Cranial and Paracranial Lesions (Tumours, Aneurysms, Thrombosis and Disseminated Sclerosis)

Tumours.—Where no other cause can be found the possibility of a tumour must be considered. Recent knowledge indicates that many of the tumours of the trigeminal ganglion described in the literature and originally thought to be primary, are due to malignant naso-pharyngeal tumours. These may infiltrate and involve the ganglion or metastasize into the base of the skull and adjacent parts. Godtfredsen (1947) who has collected 454 cases of this infrequent tumour states that ophthalmo-neurological symptoms have occurred in 34·8% of cases four or five months before diagnosis has been made, and in 70% of these the first symptom is trigeminal neuralgia in the maxillary area. The clinical features arising from tumour involvement of the trigeminal ganglion have been described by Trotter (1911), Cushing (1920) and Jefferson (1955). The pain is intense and unremitting, in distinction from the quick paroxysms of trigeminal tic. There is usually unilateral paræsthesia of a cutaneous area and sometimes of the soft palate. Sometimes there may be paralysis or wasting of the muscles of mastication on the affected side. Occasionally there may be encroachment on the oculomotor and abducent nerves causing oculomotor palsies, or on the auditory nerve causing monaural deafness.

Central tumours may cause a widespread neuralgia often associated with hemi-analgesia; also there may be signs of intracranial pressure such as choked disc, vertigo, vomiting and headache.

Secondary glossopharyngeal neuralgia may be due to a tumour or inflammatory exudate involving the nerve and in this case the pain, though subject to exacerbation, eventually becomes more of an aching type and continuous (Cohen, 1937). This differentiates it from glossopharyngeal tic. The pain occurs in the side of the throat, base of the tongue and back of the ear. There may also be other signs of nerve involvement.

Intracranial aneurysms and thrombosis.—Intracranial aneurysms adjoining the trigeminal nerve are a rare cause of neuralgia. There are varying other pressure symptoms depending on the site of the aneurysm and which other nerve or nerves are involved.

Aneurysms of the internal carotid artery within the cavernous sinus.—The internal carotid artery lying in the carotid groove is, together with the carotid plexus, embedded in the cavernous sinus. In this region the first two divisions of the trigeminal nerve, the oculo-motor and trochlear nerves are embedded in the lateral wall of the cavernous sinus while the abducent nerve is within it. Saccular aneurysms of the artery that later occasionally burst into the cavernous sinus were first described as a group by Jefferson (1938, 1953), who has reported 38 cases, nearly all in elderly females. There may be compression symptoms on the first division of the trigeminal nerve or on the first and second divisions or on the whole nerve. The pain is very severe and continuous and numbness frequently occurs. In addition, one or all of the three motor nerves of the eye may also be compressed, with consequent nerve palsies. Some of the symptoms and signs may be transient.

Thrombosis of the posterior inferior cerebellar artery.—Harris (1950) reports that this is a rare cause of intractable unilateral facial neuralgia. The lesion causes sclerosis of part of the medulla involving the descending spinal root of the trigeminal nerve (uncrossed) and of the spinothalamic ascending sensory tract (crossed), resulting in hypæsthesia or paræsthesia of the face on the side of the lesion, and on the opposite side of the body below the face. Pain may occur in both these areas.

Disseminated sclerosis.—Harris (1950) states that approximately 4% of his cases of trigeminal neuralgia had the complication of disseminated sclerosis. Usually the spinal symptoms occur before the neuralgia, but occasionally the neuralgic tic may precede the symptoms of the disease by several years.

Bilateral trigeminal tic is rare but he has found it occasionally in disseminated sclerosis, which suggests that the scattered patches of sclerosis are apt to irritate the spinal trigeminal roots on both sides. Klemme (1951) reports 14 bilateral cases of neuralgia out of more

than a thousand cases of disseminated sclerosis, but in only 2 were both sides simultaneously affected.

Causalgia

Ætiology.—The term causalgia (καυσος burning, αλγος pain) was introduced by Mitchell (1872) to describe the pain that sometimes occurs in the stump of an amputated limb. Rarely, following this operation, the phantom limb is experienced. The pain occurs some time after injury to the sensory peripheral nerve fibres in the region supplied by the nerve, though the original injury may apparently have healed normally. It would appear to be rare for causalgia to follow dental extractions according to the writer's experience and in view of the comparatively few cases that are recorded following this very frequent operation, though Berhman (1949) states that he has observed 10 and Elfenbaum (1954) considers that 30 cases may have come within this category.

The mechanism is not altogether clear: Behrman found that neither cocaine block of the inferior dental nerve nor alcohol block of the appropriate division of the V nerve proved effectual. Previously, Bingham (1947) reported 2 cases of war injury of the cheek with subsequent continuous facial pain; these were cured by excision of the lower half of the superior sympathetic ganglion. This indicates that sympathectomy interrupts the sensory pathways, but this operation is successful in only 40% of cases in other regions.

Clinical features.—The pain, which commences days or several weeks after the original operation, is of a continuous burning nature and there is cutaneous hyperalgesia.

Neuralgia of Psychogenic Origin

Psychogenic pains are usually constant though the intensity may vary. The position of the pain may shift from time to time and it usually does not conform to the distribution of a particular nerve.

Individuals with psychogenic pains are usually female and are neurotic, emotional and complain of many bodily ailments and pains. These patients attend with minor disturbances that would be borne without complaint by the majority of people. If, however, the pain remains fairly constant in its distribution, it should not be labelled as psychogenic until all possible causes have been explored. Cohen (1952) gives helpful positive features about these types. Engel (1951) gives a detailed description of 20 cases. However, Dott (1951) has not seen one case of true psychogenic pain.

In conclusion, the importance of diagnosing the cause of an obscure facial neuralgia must be stressed, and particularly in view of the possibility of it being due to early tumour formation, even though this is comparatively rare. In such cases it is necessary to have the co-operation of the dental surgeon, otorhinolaryngologist, neurologist, and radiologist.

The writer wishes to express his gratitude to Mr. D. J. Kidd, who prepared five coloured diagrams which, unfortunately, cannot be reproduced owing to lack of space. Figs. 4 and 5 are reproduced from Stones (1954) "Oral and Dental Diseases" 3rd edit. Publishers, E. & S. Livingstone, Edinburgh, pp. 86, 625.

REFERENCES

Bauer, W. H. (1940) *J. dent. Res.*, **19**, 297.
Behrman, S. (1949) *Brit. dent. J.*, **86**, 197.
Bingham, J. A. W. (1947) *Brit. med. J.*, i, 804.
Brashear, A. D. (1936) *J. Amer. dent. Ass.*, **23**, 662.
Brookhart, J. M., Livingston, W. K., and Haugen, F. P. (1953) *J. Neurophysiol.*, **16**, 634.
Campbell, A. M. G., and Lloyd, J. K. (1954) *Lancet*, ii, 1034.
Campbell, J. (1955) *Dent. Practit.*, **5**, 175.
Cawthorne, T. (1951) *Proc. R. Soc. Med.*, **44**, 1033.
Coburn, D. F., and Shofstall, C. K. (1941) *Arch. Otolaryng., Chicago*, **33**, 663.
Cohen, H. (1937) *J. Laryng.*, **42**, 527.
—— (1952) In: British Encyclopædia of Medical Practice. 2nd edit. London; **9**, 365.
Cook, W. T. (1949) *J. oral. Surg.*, **7**, 149.
Costen, J. B. (1934) *Ann. Otol. Rhin. Laryng.*, **43**, 1.
Cushing, H. (1920) *Amer. J. med. Sci.*, **160**, 157.
Dott, N. M. (1951) *Proc. R. Soc. Med.*, **44**, 1034.
Douglas, B. L. (1953) *Oral Surg.*, **6**, 1199.
Douglas, T. E. (1952) *Arch. Otolaryng., Chicago*, **56**, 635.
Eagle, W. W. (1937) *Arch. Otolaryng., Chicago*, **25**, 584.
—— (1942) *Arch. Otolaryng., Chicago*, **35**, 66.
—— (1948) *Arch. Otolarygn., Chicago*, **47**, 630.
Elfenbaum, A. (1954) *Oral Surg.*, **7**, 594.
Encel, G. L. (1951) *Psychosom. Med.*, **13**, 375.
Fay, T. (1932) *Ann. Otol. Rhin. Laryng.*, **41**, 1030.

FENICHEL, N. M. (1948) *Ann. intern. Med.*, **29**, 456.
FRITZ, M. (1940) *Arch. Otolaryng., Chicago*, **31**, 911.
GLASER, M. A., and BEERMAN, H. M. (1938) *Arch. intern. Med.*, **61**, 172.
GODTFREDSEN, E. (1947) *Proc. R. Soc. Med.*, **40**, 131.
GRANT, F. C. (1935) *Amer. J. Surg.*, **27**, 430.
HARDY, J. D., WOLFF, H. G., and GOODELL, H. (1940) *J. clin. Invest.*, **19**, 649.
HARRIS, W. (1921) *Brit. med. J.*, ii, 896.
—— (1936) *Brit. med. J.*, i, 457.
—— (1950) *Brit. med. J.*, ii, 1015.
HILGER, J. A. (1949) *Laryngoscope, St. Louis*, **59**, 829.
—— (1950) *Bull. Univ. Minn. Hosp.*, **22**, 153.
JAEGER, R. (1946) *Arch. Otolaryng., Chicago*, **44**, 424.
JEFFERSON, G. (1937) *Brain*, **60**, 444.
—— (1938) *Brit. J. Surg.*, **26**, 267.
—— (1953) *Trans. ophthal. Soc., U.K.*, **73**, 117.
—— (1955) In: Clinical Neurosurgery. Editor: Raymond K. Thompson. Baltimore; Vol. **1**.
——, and SCHORSTEIN, J. (1955) *Brit. J. Surg.*, **42**, 561.
KARL, R. C., PEABODY, G. E., and WOLFF, H. G. (1945) *Science*, **102**, 12.
KLEMME, R. (1951) *J. Mt. Sinai Hosp.*, **17**, 729.
MCAULIFFE, G. W., GOODELL, H., and WOLFF, H. G. (1943) *Proc. Ass. Res. nerv. Dis.*, **23**, 185.
MACGREGOR, A. B. (1955) The Treatment of Fractures of the Mandibular Condyle (Charles Tomes Lecture, Royal College of Surgeons of England).
MITCHELL, S. W. (1872) Injuries of Nerves and Their Consequences. Philadelphia.
PFAFFMANN, C. (1939) *J. Physiol.*, **97**, 220.
ROWBOTHAM, G. F. (1954) *Lancet*, i, 796.
SICHER, H. (1944) *Bur*, **44**, 91.
SJÖQVIST, O. (1938) *Acta Psychiat., Kbh.*, suppl. 17.
—— (1948) *Brasil méd.*, **10**, 259.
SLUDER, G. (1918) *South. med. J.*, **11**, 312.
STONES, H. H. (1954) Oral and Dental Diseases. 3rd edit. Edinburgh: p. 775.
STRONG, D. S., and ELWYN, A. (1953) Human Neuroanatomy. 3rd edit. Baltimore; p. 243.
TAARNHØJ, P. (1952) *J. Neurosurg.*, **9**, 288.
TATLOW, W. F. T. (1952) *J. Neurol. Psychiat.*, **15**, 45.
TROTTER, W. (1911) *Lancet*, i, 1277.
VAIL, H. H. (1932) *Ann. Otol. Rhin. Laryng.*, **41**, 837.
WATTS, F. B. (1951) *Ann. intern. Med.*, **35**, 186.
WOLFF, H. G. (1948) Headache and Other Head Pain. London.
WRIGHT, S. (1952) Applied Physiology. London; p. 571.
WYBURN-MASON, R. (1953) *Brit. med. J.*, ii, 119.
ZAMORA, A. M. (1951) *J. Laryng.*, **65**, 664.

BOOK REVIEWS

Dextran: Its Properties and Use in Medicine. By John R. Squire, M.D., F.R.C.P., J. P. Bull, M.D., W. d'A. Maycock, M.D., and C. R. Ricketts, Ph.D., F.R.I.C. (Pp. 91; 7 figs. 15s.) Oxford: Blackwell Scientific Publications. 1955.

The clinical use of dextran as a plasma substitute is becoming established and the production of a monograph detailing its properties and clinical uses is to be welcomed. After a short chapter on the properties required in plasma substitutes and the conditions under which they should be used, the chemistry and physical chemistry of the dextrans is discussed, and this is followed by a short description of the methods on which the commercial preparation of the dextrans are based. This leads naturally to a careful description of the properties of the clinical dextrans and their behaviour in the body. The section on immunity reactions, including the discussion of the serological relationships between native and clinical dextrans and certain pneumococcal rabbit antisera, is of great interest, more especially in connexion with their possible relationship to some of the side-effects observed in man. While allowing the possibility of immunity type reactions being involved in some of the side-effects it is of interest to note that the authors do not consider the possibility of histamine relapse, such as Halpern observed with dextran in the rat as being a factor, and yet they report that some of the side-effects in man are ameliorated by the use of antihistamines. No doubt subsequent investigation will clear up this point. The account of the clinical uses of dextran is well balanced—"dextran is effective as a plasma volume expander in states of shock". Due stress also is laid on the danger of over-correction of a fluid loss and consequent overloading of the circulation. The use of dextran for the relief of nephrotic œdema is also described. The final chapter deals with the experimental uses of dextran as a means of studying the action of macro-molecules and their relation to permeability and other problems. Mention is made of certain charged derivatives of dextran, mainly to point out that their properties are different, e.g. the dextran sulphates have considerable anticoagulant activity not possessed by the dextrans. Apart from an obvious error in the pyranose ring formula in Fig. 1(*b*) the monograph is free from misprints. It is an essential book for users of dextran. The authors are to be congratulated in summarizing their experiences in such a useful and readable fashion.

Differential Diagnosis: The Interpretation of Clinical Evidence. By A. McGehee Harvey, M.D., and James Bordley III, M.D. (Pp. xiv+665. 77s.) Philadelphia and London: W. B. Saunders Co. 1955.

This book is based on the records of carefully selected clinical/pathological conferences held at the Johns Hopkins Medical School, together with a few from the Mary Imogene Bassett Hospital. The technique of diagnosis which the authors discuss is therefore that of the conferences, namely, collecting all available information about the patient, sifting it and then reaching a conclusion as a result of careful reasoning.

This is, of course, an admirable method, and one which is properly taught to the student at the bedside as a part of his basic education. It is, however, extravagant of time, and many experienced clinicians only employ it in practice when they are confronted with a problem of great diagnostic difficulty. They prefer rather to start attempting to build up a diagnosis from the moment they greet the patient.

The authors have selected a number of commendably common symptoms as a starting point for their discussion of the method of building up a differential diagnosis, and from it, a diagnosis. They illustrate their points with case histories, complete with clinical details and examination, a record of the investigations that were carried out, an analysis of those that were considered relevant and a discussion of the diagnosis. This is followed by a description of the anatomical findings at autopsy and a summary of the whole case history and of the lessons to be learned from it.

The material available to the authors is extensive and the care that they have taken in selection is evident. "Jaundice", "Hæmatemesis", "Pain in the Chest" and "Sudden Death" are all examples of chapter headings. Tables have been introduced to indicate a framework for the grouping of conditions which present with some of the symptoms which are under discussion, and these are for the most part both simple and helpful.

The difference in diagnostic problems, as well as in the methods of resolving them, in the States as compared with Britain is of interest. Some stress, for instance, is laid on gonococcal endocarditis, a condition rarely encountered over here. "Main line shooters" are also news to most of us, and are drug addicts, chiefly inhabiting seaports, who, by using a common syringe, may pass malaria from one to the other.

The last chapter gives the case histories of 11 patients in such a manner that the reader can place himself in the position of the physician who was asked to discuss them at the clinical/pathological conference. This is to say they are given all the information that was available to him, namely, the findings and the opinions expressed during life, and at the end

of the chapter there is the answer in the form of the anatomical findings and discussions which took place at the actual conference.

The solution of these problems has a similar entertainment value to crossword puzzles to a certain type of mind, and provided that it is realized that the reader is carrying out an intellectual exercise, their study will be helpful as well as entertaining. If, however, this method of diagnosis is accepted too readily, there is a real danger that the clinician may turn from the bedside to the armchair and lose the diagnostic inspiration that can only arise from close contact with patients.

Medical Students and Medical Sciences: Some Problems of Education in Britain and the United States. By D. C. Sinclair, M.A., M.D. (Pp. xii+154. 25s.) London, New York, Toronto: Oxford University Press (Geoffrey Cumberlege). 1955.

Talk of reforms in medical education is perennial. Most teachers have an uneasy feeling that education could be improved but no one has very clear ideas as to the means. Dr. Sinclair does not claim to solve the problem in his witty and thoughtful book, "Medical Students and Medical Sciences", but he puts many of the problems more succinctly than they have been put elsewhere, particularly those concerning the preliminary subjects of the curriculum although much of what he says has a more general application.

There are at least two ways of dealing with the constantly expanding field of knowledge in the medical sciences. One method, and that still followed at most schools, is the pursuit of new knowledge while retaining all the old. It is this method of study which is breaking down and which leads to demands for lengthening the period of study still farther. The second method is to give up the unequal struggle and prune the curriculum down to the essentials leaving the more advanced theoretical studies for after qualification.

Dr. Sinclair says "I realize that a lot of nonsense is talked about the preclinical sciences being disciplines in themselves—it may be true but it is none the less irrelevant for the medical student who wants to become a fully educated doctor and not a partly informed scientist."

Medical education must be largely vocational. Clinical education would be nonsense if it were not; but subjects are taught in some schools as if the teachers had no idea that the students were to be students of medicine. Dr. Sinclair specially mentions biochemistry and says "To one who is not a biochemist it must often appear that the biochemistry department is more out of touch with the aims of the medical school than any other preclinical science. The content of some biochemistry courses does not suggest that the needs of the medical student have been in any way consulted; . . . Biochemistry . . . occupies in some medical schools the position which anatomy formerly held—a position from which inordinate scientific detail is regarded as the best training for the embryo doctor. Instead of memorizing the facets on the carpal bones, students are now required to remember the steps of steroid synthesis in the liver". Many biochemists fail to realize that it is possible to be quite a good doctor with little or no knowledge of steroid chemistry, or a very bad one with a full comprehension.

Dr. Sinclair describes experiments in medical education in the United States and makes out a case for experiment here. He also touches on the vertical method of teaching the medical sciences contrasted with the horizontal method. It is to be regretted that the University Grants Committee prevented the trial of the vertical integrated curriculum in London University.

Dr. Sinclair examines various systems of examination and describes the so-called objective type of examination in use in some schools in the United States and threatened occasionally in this country. Whatever the theoretical advantages or disadvantages of this system as a method of registering factual knowledge one views it with what may only be old-fashioned prejudice, but there are already many complaints that modern-method students can neither write nor spell and it seems an unhappy solution of this problem to evolve a system by which all he has to do is make his "mark". Dr. Sinclair's book is enjoyable, both provocative and entertaining, and is very profitable reading for anyone interested in medical education who has not adopted the second quotation from the front of the book.

"It were better to perish than to continue schoolmastering."

The Mayo Clinic. By Lucy Wilder. Illustrated by Ruth Barney. 2nd edition. (Pp. 71. 27s. 6d.) Oxford: Blackwell Scientific Publications. Springfield, Ill.: Charles C. Thomas. 1955.

Mrs. Wilder's book was written twenty years ago, in response to a request by patients to tell them "something about the Mayo Clinic". It is a friendly and conversational guide to the first and most famous private medical institution in the world.

William Worrall Mayo, a young graduate in chemistry from Manchester, emigrated to

the United States in 1845. He worked as a chemist in New York, studied medicine and qualified in Indiana and, after serving in the Civil War, he moved in 1863 to Rochester, Minnesota, where he started to practise medicine. Here he trained his sons, William and Charles who were born in 1861 and 1865, teaching them osteology on the skeleton of the Indian Chief Cut Nose, who was executed after the Sioux rising in 1862.

In 1883 a cyclone struck Rochester, killing twenty-two and injuring many more. Dr. Mayo was appointed by the city to attend the injured, and was helped by Sisters from the Convent of St. Francis. From this disaster, and from this happy collaboration, sprang the Mayo Clinic. In 1889 the Hospital of St. Mary with forty beds, built by the Order of St. Francis on ground given by Dr. Mayo, was opened with a staff consisting of the Doctor and his two sons. The Clinic has grown round St. Mary's Hospital and the Mayo family. The Hospital, owned and managed by the Order of St. Francis and constantly enlarged, remains the chief ward block and the centre of surgical work. The Mayo brothers, William and Charles, worked together in Rochester for fifty years, and became the most famous surgical partnership in the world. William's sons-in-law, Donald Balfour and Waltman Walters, and Charles's son, Charles Mayo junior, are to-day central figures in a staff of several hundred that deals with every branch of medicine and surgery.

This book will interest not only patients of the Clinic, but all surgeons who know or who hope to visit it. The writing is intimate and personal. The illustrations include one of the bronze group of the famous brothers, a map of the simple street plan of Rochester, and a photograph of the Clinic building from whose roof one can look in every direction on the cornfields that surround the tiny town that is the Mecca of world surgery.

An Introduction to Psychiatry. By Max Valentine, M.D., D.P.M. (15s.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

Dr. Valentine has set out to achieve some sort of integration between psychiatry and the remainder of medicine in the way that psychiatry is thought about; and to make the subject less foreign to a student whose training has been in the biological sciences. There is no doubt that he has been successful in his first few chapters, and his account of behaviour as an adaptation achieved by homeostatic stabilizing mechanisms is clear and eminently readable. For this reason alone the book deserves to succeed but it will require considerable expansion if it is to be of use to the medical student and general practitioner for whom it is presumably intended. An irritating decimal subdivision has replaced ordinary page numbering, but the book appears to have about 300 pages of big print. The main part of the book, which deals with the syndromes in the usual way, is not adequate in many places. Thus when dealing with the question of terminating pregnancy on psychiatric grounds, the author says in effect that the problem is a complex one and leaves it at that.

There are a few errors. On the last of the six pages labelled 2.1.2. "infinite" should read "infinitesimal". The law relating to contract and tort is incorrectly stated. Thus a contract made when a person is insane is not void as the book states. It is *voidable* provided that the other party knew of the insanity when the contract was made. Similarly it is stated that those of unsound mind are incapable of committing torts and this is not true.

There is a useful section on intelligence testing and on elementary statistics though both are too condensed to be easily followed by the student. The index appears adequate and the book is pleasingly produced.

The Plasma Proteins in Pregnancy. A Clinical Interpretation. By Harold C. Mack, M.D. (Pp. xii+118; illustrated. 27s. 6d.) Oxford: Blackwell Scientific Publications. Springfield, Ill.: Charles C. Thomas. 1955.

This addition to the American Lecture Series of monographs is concerned with the changes in plasma proteins in normal and pathological pregnancies, and their possible relationships to the various adaptations occurring in this state. The author is a clinician and the accent is on clinical aspects of the subject. The analyses consist of a series of electrophoretic measurements of the proteins of maternal and fœtal bloods. No other methods of investigation have been used.

After a brief introduction about some of the physicochemical properties of plasma proteins the discussion proceeds to the changes which occur in them in normal pregnancies, toxæmias of pregnancy and finally pregnancies complicated by a variety of other diseases. One is left at the end of 100 pages with the impression of a number of minor quantitative changes in plasma proteins occurring without much physiological background, and with a few exceptions the clinical bearing of these changes is not obvious. The last chapter on the relationship between fœtal and maternal blood proteins is perhaps the most interesting, but the discussion of the placental barrier is short and nothing said of the protein changes in erythroblastosis fœtalis. At the end of the book is a lengthy bibliography for further reading. The impression left is that of a picture without much meaning. It would seem to

be a book clearly written, but of value only to those interested in this specific application of plasma proteins.

The Princes in the Tower and other Royal Mysteries. By Sir Arthur Salusbury MacNalty, K.C.B., M.A., M.D.Oxon, F.R.C.P., F.R.C.S. (Pp. 212. 18s.) London: Christopher Johnson. 1955.

This book contains a medley of mysteries in high life, of considerable criminological and medico-legal interest. The account of the murder of the Princes in the Tower, which gives the main title to the book, only occupies 16 pages and contains very little that is new. Other sections deal with the crimes of King Philip II of Spain, the eccentricities of ex-Queen Christina of Sweden, the tragedy of Peter the Great and his son Alexis, the remarkable career of Queen Caroline Matilda of Denmark, and the varying fortunes of the adventuress Sophy Dawes. The sad story of Henrietta, Duchess of Orleans, who died from a perforated gastric ulcer, is also related. In every case the author sums up the case with judicial impartiality and leaves us in no doubt as to his opinion. Needless to say the style is clear and interesting and each chapter has the chief references appended to it.

By those who like murder mysteries with a medical flavour this book will be welcomed, but it will not raise their opinion of their fellow-mortals.

The Pathogenesis of Poliomyelitis. By Harold K. Faber, M.D. (Pp. xvi+157; 16 illustrations. 36s.) Oxford: Blackwell Scientific Publications. Springfield, Ill.: Charles C. Thomas. 1955.

The publishers claim on the cover of this monograph that it "explains the *modus operandi* of poliomyelitic infection". Lest anyone be misled into accepting this claim, it may be said at once that it does no such thing: it is a short review of Dr. Faber's personal views on the pathogenesis of this disease which differ in many respects from those held to-day by most students of this subject. The volume is also the more concise because the author makes little mention of much of the relevant work on neurotrophic viruses carried out by other investigators in the United States and virtually ignores the contributions of Europeans.

Dr. Faber accepts the commonly current view that the alimentary tract is the main portal for the responsible virus. But he soon parts company with most contemporaries who believe that the local invasion of the wall of the alimentary tract is followed by an initial viræmia, for he upholds the older conception that the virus, after gaining entry through the mucosa of the mouth or pharynx, passes centripetally by way of regional nerves, first to local ganglia and thence to the central nervous system. These peripheral ganglia form not only the primary site for the multiplication of the virus, but also the source from which it returns by centrifugal axonal spread to maintain a persistent excretion into the lower alimentary tract. He thus regards the viræmia, which is now recognized as a common occurrence in human poliomyelitis, as a relatively late manifestation that results from the passive absorption of virus from the intestines in amounts that exceed the phagocytic defensive powers of the reticulo-endothelial system.

The possibility of transportation of certain toxins and viruses to the brain and spinal cord along the axoplasm of nerve fibres has often been canvassed but never demonstrated. Indeed, modern studies on the protoplasmic structure of axons have rendered this hypothesis less and less inviting. Dr. Faber has offered no new observations that could provide a basis for reconsidering this possibility, nor has he made any suggestion as to a physiological mechanism by whose operation this hypothetical transportation, rapidly, for long distances and over tortuous routes, could be brought about.

Although in this monograph, Dr. Faber has nailed his colours to the mast with a certain defiance, it should not be supposed that he has done so without a full appreciation of the complexities of the issues raised. During the past twenty years, he and his collaborators in California have undertaken very pertinaciously a long series of carefully conducted experiments in this important field of neuropathology. Even if many readers are unable fully to accept his conclusions, they should be grateful to him for a clear and provocative statement of his position. For this book is, and was probably intended by the author to be, essentially an expression of his personal views by a partisan in an important current controversy.

Vitamins in Theory and Practice. By Leslie J. Harris, Sc.D., D.Sc., Ph.D., F.R.I.C. 4th edition. (Pp. xxii+366; 103 illustrations. 35s.) Cambridge: Cambridge University Press. 1955.

This is the fourth edition of Dr. Harris's book. The original arose out of four lectures, but the present volume well indicates the very great increase in knowledge. This has somewhat upset the balance of the book. Much of it is written for the non-medical reader and is well suited for an intelligent layman but the newer work needs a background of

knowledge which an average layman does not possess and Dr. Harris has found it necessary to step aside from his main theme at times to try and supply some of this knowledge. For the medical reader this makes the book at times tedious and unnecessarily long, but for the growing group of non-medical workers in other disciplines this book should supply an easily read and authoritative account of the history and present knowledge of the various vitamins.

The pattern of the book follows traditional lines—initial chapters on the discovery of vitamins and vitamins in general, followed by chapters discussing each individual vitamin and the disease associated with its absence. Besides the usual well-recognized vitamins, the late chapters include all the other vitamins and similar dietary factors, such as choline, which are needed in animal nutrition. There is a noteworthy restraint in claiming pathological or therapeutic effects for this rather less known group and the differences between man and experimental animals are stressed.

This book is not intended for the medical research worker, but for the student, qualified or unqualified, who wishes to take his dose of vitamin in jam, it can have no rival.

Introduction to Hepatic Surgery. By Henry Gans, M.D. (Pp. xvi + 265; 120 figs. 70s.) London: Cleaver-Hume Press Ltd. Amsterdam, &c.: Elsevier Press, Inc. 1955.

Dr. Gans reviews the literature of the intimate structure of the liver and of the detailed anatomy of the biliary apparatus and the hepatic circulation. He adds a great deal of careful personal anatomical work, conducted largely by the injection-corrosion technique, and endeavours to correlate his findings with those of others in planning a subdivision of the liver into units or segments, as has been done by Brock in the case of the lung. In the second half of the book he discusses the indications for operations on the liver, and endeavours to outline a series of segmental resections based on the unities he has described.

This book is in the nature of an essay or thesis rather than a textbook of operative technique. The work is painstaking and thorough, the illustrations of the corrosion specimens are admirably reproduced, and Dr. Gans does his best to make the subject as clear to others as it is to him. The more, however, he goes into detail, the more confusing does that detail become, the more is it obvious that the various subdivisions of the Glissonian and venous systems are not accompanied by any clear boundaries on the surface, or even in the substance, of the liver.

Certain simple and important facts that are already known, but not widely, are confirmed. The liver consists of two halves, anatomically distinct, but the boundary between them is not the anatomical division of the liver into right and left lobes, but an invisible and impalpable plane that passes from the gall-bladder fossa in front to the left of the fossa for the inferior vena cava behind. There is no anastomosis of any kind between the biliary systems of the two halves in the liver itself, so that Longmeyer's operation has no rational basis. There are occasional anastomoses in as well as outside the liver between the right and left hepatic arteries, a fact that may explain the occasional survival after accidental ligature of the right hepatic artery. As well as these facts, the old fairy-tale about a separate stream for the splenic and the mesenteric blood in the portal vein is repeated.

The anatomist will be interested in this book. The surgeon is unlikely to buy it or read it unless he has a patient presenting one of the uncommon indications for a planned segmental hepatectomy.

Neurochemistry. The Chemical Dynamics of Brain and Nerve. Thirty-two articles written by experienced investigators in their respective fields. Edited by K. A. C. Elliott, M.Sc., Ph.D., Sc.D., Irvine H. Page, M.D., and J. H. Quastel, D.Sc., Ph.D., F.R.C.S., F.R.S. (Pp. xii+900; illustrated. £7.) Oxford: Blackwell Scientific Publications. Springfield, Ill.: Charles C. Thomas. 1955.

Although, at first sight, it may seem an unnecessary addition to an age of increasing specialization to dignify the study of the biochemistry of the brain with the title of Neurochemistry, yet it is true, as this book reveals, that an understanding of the biochemical processes occurring in the nervous system is of far-reaching importance. Many of the advances in the fields of vitamin and trace element deficiency diseases, and in our knowledge of certain psychiatric disorders, as well as of the mechanism of narcosis and the action of insecticidal chemicals, are dependent on the developing picture of this section of biochemistry, or have indeed contributed to it.

The publication of a book of some 900 pages describing the chemical dynamics of brain and nerve, by 32 contributors, each a specialist in his own section of this complex field, is therefore likely to be welcomed by a wide range of readers.

This book is not a narrow account of the "pure" biochemistry of the brain. The subject is dealt with from many angles, and the physiological aspects are particularly well covered. In addition to a series of informative chapters on the chemical constituents of nervous tissue, its glycolytic and oxidative mechanisms, the metabolism of pyruvate, glutamate,

glutamine and acetylcholine, there are included stimulating accounts of the biochemistry of the brain during early development, electrolytes and nerve function, intracranial fluids and the blood-brain barrier, blood flow and metabolism in the human brain in health and disease, "neurotropic" drugs, bacterial neurotoxins, the effects of snake venoms, the toxic effects of oxygen, narcosis, convulsive conditions, demyelination, nutritional disorders and inborn errors of metabolism.

In general the authors have given a clear and critical account of our present knowledge of this rapidly growing subject, although it is a pity that the story of vitamin B_{12} and subacute combined degeneration of the cord is dismissed in only 14 lines. The editors are to be congratulated, however, both on the scope covered by this book and on their selection of contributors. Some of the views that are expressed, particularly concerning the functional significance of certain aspects of brain biochemistry, will not be accepted by all, but it is useful to have these views included in a book of this type, which, with its ample bibliography, will be of value to a wide range of investigative workers and senior students.

It must be added that in these days of concentration on the present rapid growth of science, it is a pleasure to find that the book is dedicated to the memory of Thudichum, and includes a chapter telling us something of the life and work of this remarkable pioneer in the field of neurochemistry.

Clinical Toxicology. By Clinton H. Thienes, M.D., Ph.D., and Thomas J. Haley, Ph.D. 3rd edition. (Pp. 457; illustrated. 48s.) London: Henry Kimpton. 1955.

Information on clinical toxicology is usually buried in textbooks of pharmacology or medical jurisprudence, and quick reference to such problems may be difficult. This book, however, deals with the subject as a whole including diagnosis, clinical and chemical, and the symptomatology and treatment of poisoning. The number of cases of poisoning any practitioner may come across may not be large, but the possibility of such cases arising is greater than ever before. This book has been designed as a classroom text and as a guide to the general practitioner. It can serve as both. Outside the immediate diagnosis and treatment of the acute episode, most of the material treated is more useful to the expert, and in this country at least it is doubtful whether any practitioners would go so far as to undertake the detection and estimation of the toxic materials. Nevertheless, a knowledge of the action and modes of excretion of poisons is essential to any method of treatment or detection, and much valuable information and time may be lost if these fundamental principles are not understood. The first half of the book is devoted to symptomatology and treatment under various headings. Most of the recent improvements in treatment are given their place, e.g. the use of BAL in metallic intoxications and nalorphine for the morphine type of poisoning. For British readers the fact that many drugs are given their American names may be a disadvantage e.g. ergonovine for ergometrine. Most of the subject matter has been brought up to date, but there is a correction for future editions, on page 138 Barger should not have been quoted as saying convulsive ergotism was most frequently found in Germany, and the gangrenous type in France and Russia; gangrenous ergotism has not been common in Russia. A considerable number of the most recent drugs are mentioned including a number of the antihistamines, the newer morphine-like types, phenylbutazone, and the curare types, and the possible uses of folic acid, pyridoxine and liver extract are considered for poisonings of the blood and hæmatopoietic organs. The general principles of treatment, and symptomatic diagnosis, are also dealt with in a useful summary. The section on the detection and estimation of poisons is very detailed including the standard well-known methods, plus considerable details for the new drugs, in many cases with useful indications of the sensitivity of the reactions used. The authors have searched the scattered literature thoroughly. The book therefore gives a satisfactory survey of the present state of toxicology, and will be of value to those interested in treatment and detection of poisoning, industrial or accidental.

The Boke of Chyldren. By Thomas Phaire. (Pp. 76. 7s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

A fascinating book—fascinating to dip into, fascinating to read from cover to cover. The first "boke" on pædiatrics written by an Englishman and one of the earliest medical books to be printed in the English language, it appeared first in 1545. This is an exact copy of the 1553 edition in the University of Bristol Medical Library, with a delightful introduction and foreword by Professor A. V. Neale and Dr. H. R. E. Wallis, and a useful glossary. "Studiouse in Philosophie & Phisicke," Thomas Phaire (like Shakespeare he spelt his name in several ways) was a medical pioneer, a keen observer, and a quaint and intriguing writer. The section titles are often sufficient to stimulate the appetite for reading: "an excellent remedy for wartes or knobbes of the head"; "of bloud shotten eyes, and other infirmities"; "of colicke and rumblying in the guttes"; "of pissing in the bedde"; "of fallyng of the fundament"; "of lise".

Proceedings of the Royal Society of Medicine Vol. 49 55

Section of Pathology

President—Professor L. P. GARROD, M.D., F.R.C.P.

[*October* 18, 1955]

The Immune-adherence Phenomenon

A Hypothetical Role of Erythrocytes in Defence against Bacteria and Viruses

By ROBERT A. NELSON, Jr., M.D.

Associate Professor of Microbiology, Yale University School of Medicine; Investigator for the Howard R. Hughes Medical Institute

IN 1953 the phenomenon of immune-adherence (I-A) was described as an *in vitro* immunological reaction between normal erythrocytes (red blood corpuscles; r.b.c.) and a wide variety of micro-organisms sensitized with their individually specific antibody (Ab) and complement (C′) (Nelson, 1953). These experiments showed that the union or adherence of the bacteria to erythrocytes led to an enhancement of phagocytosis of bacteria by leucocytes.

The only preceding evidence of such a phenomenon involved two reports on the so-called Rieckenberg phenomenon, one by Leupold from Germany in 1928, the other, an extension of Leupold's findings by two British workers, Duke and Wallace, in 1930. Both these reports concerned the adhesion of sensitized trypanosomes to platelets, to bacteria, and to r.b.c. No mention was made in either report of phagocytosis. Subsequent work on these organisms suggested that the adhesion phenomenon was not specific immunologically but instead was a function of the electric charge of the particular strains of trypanosomes employed (Broom *et al.*, 1936).

Very recently, evidence has been obtained which indicates that I-A occurs *in vivo* in monkeys injected with certain bacteria. It is this aspect of the work which will be emphasized in this report.

The overall results have led to the formulation of a "working" hypothesis that the erythrocyte may function as an opsonizing agent *in vivo* as it does *in vitro*, and therefore may be considered as a part of the host's mechanism for defence against microbial invasion.

To provide a criterion for a critical analysis of the experimental results to be presented, the general hypothesis may be stated briefly in terms of the following three premises:

Premise 1. The entrance of bacteria (B) into the blood stream of individuals possessing circulating antibody (Ab) and complement (C′) is followed by the formation of the complex B-Ab-C′. In certain species this complex becomes attached to the surface of r.b.c. via immune-adherence (I–A). By analogy to *in vitro* experiences, the susceptibility of the adherent B–Ab–C′ complex is markedly increased as compared to that of the B–Ab–C′ which is floating free in plasma. *Therefore the erythrocyte may be considered as an opsonic agent for bacteria in an immune host whose erythrocytes are reactive in I–A.*

Premise 2. The entrance of certain viruses into the blood of non-immune individuals is followed by the well-known adsorption of the virus to the surface of the r.b.c. This adsorption is reversible. While the virus is on the r.b.c. surface, it may be more susceptible to phagocytosis than virus which is floating free in plasma. *Therefore, the erythrocyte may be considered as an opsonic agent for certain viruses in the non-immune host.*

Premise 3. Premise 1 may be restated for certain viruses which in the presence of Ab and C′ undergo I–A. *Therefore, the erythrocyte may be considered as an opsonic agent for certain viruses in an immune host whose erythrocytes are reactive in I–A.*

In order to define the status of I–A as an *in vitro* immunological reaction which is perhaps comparable with C′ fixation, agglutination, bactericidal and bacteriolytic reactions, it is necessary to mention that a wide variety of bacteria examined to date undergo I–A provided C′ and their individually specific Ab are present. Some of the bacteria which have been examined include: *Diplococcus pneumoniæ*, *Micro. aureus*, *Myco. tuberculosis*, several salmonellæ and shigellæ, two neisseria, erysipelothrix, the El Tor cholera bacillus and *Esch. coli*. In addition *Treponema pallidum*, starch granules (Nelson and Lebrun, 1956) and vaccinia virus (Nelson, unpublished) have shown typical reactivity. In a current research project, as yet unconfirmed evidence has been obtained that poliomyelitis virus undergoes I–A.

In conformity with the unitarian concept of Ab reactivity, there is evidence that the same Ab which induces precipitation with the S1 polysaccharide of *Diplococcus pneumoniæ*, also induces I–A. Removal of agglutinins to *Micro. aureus* or to several of the enteric pathogens similarly removes Ab which promotes I–A with the homologous organism. In addition,

at least qualitatively the same components of C′ which function in immune hæmolysis and in opsonization appear to be essential for I–A. This experiment was based upon the findings of Mayer and collaborators (1954) who defined the sequence of combination of C′ components to sensitized sheep erythrocytes. Our results on I–A with sensitized starch granules, shown in Table I, are tentatively interpreted to mean that all four components of C′ are required for induction of reactivity in I–A.

TABLE I.—THE FRACTIONS OF C′ REQUIRED FOR I–A BETWEEN SENSITIZED STARCH GRANULES AND HUMAN ERYTHROCYTES

Starch–Ab complex treated 15 min. with C′			Theoretical complex (after Mayer *et al.*, 1954)	Percentage of granules adherent after 45 min. (37° C.)
Ca++	Mg++	Temp. °C.		
0	0	0°	(S–Ab)	0
0	0	37°	(S–Ab)	1
·001 *M*	0	0°	(S–Ab) – C'_1 – C'_4	0
·001 *M*	0	37°	(S–Ab) – C'_1 – C'_4	3
·001 *M*	·003 *M*	0°	(S–Ab) – C'_1 – C'_4 – C'_2	1
·001 *M*	·003 *M*	37°	(S–Ab) – C'_1 – C'_4 – C'_2 – C'_3	86

The requirement for C′ has been studied further by experiments designed to demonstrate reversion of the sensitization induced by Ab and C′. Since at least two components of C′ are markedly heat labile, the influence of heating the B–Ab–C′ complex was examined. No effect on the susceptibility to I–A was noted upon heating for two hours at 56° C. On the other hand, it has been possible to reverse reactivity by treatment of B–Ab–C′ with papain. This experiment, shown in Table II, serves to negate one hypothesis of the action

TABLE II.—THE REVERSION OF SUSCEPTIBILITY TO I–A BY TREATMENT OF THE STARCH-ANTIBODY-COMPLEMENT COMPLEX WITH "ACTIVATED" PAPAIN

Treatment of starch–Ab–C′ complex	Percentage of washed granules adherent after 30 min.
Untreated	80
Cysteine only	76
"Non-activated" papain	80
"Activated" papain	1

"Non-activated" papain—solution of papain (British Drug Houses) in water, brought to pH 7·0 with NaOH.

"Activated" papain—10 ml. non-activated mixed for 30 min. with 1·0 ml. 16% cysteine neutralized with NaOH.

of Ab and C′ on bacteria, i.e. that some fundamental, non-reversible change is induced in the bacterium which provides an altered surface capable of adhering to erythrocytes. Instead, this result suggests the combination of the Ab and C′ functions in an "additive" fashion and provides the linkage between bacterium and erythrocyte. As shown in Table I, this linkage is markedly dependent upon the final step in C′-fixation, i.e. the combination of C'_3.

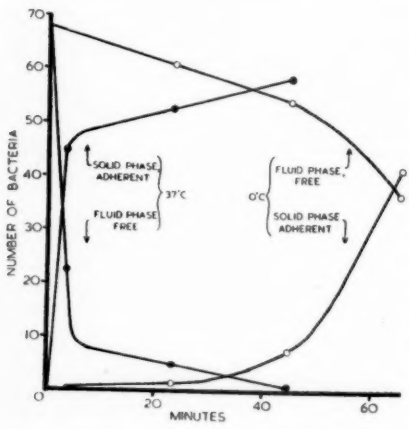


FIG. 1.—Rate of adherence of the bacterium-antibody-complement complex to erythrocytes.

There are certain other characteristics of I–A which merit mention. It would be expected that a reaction involving C′ would proceed more rapidly at 37° C. than at 0° C. However, recently it has become possible to show that the adherence *per se* is depressed at 0° C. to 2° C. In order to carry the bacteria through the C′ step, a suspension of *Micro. aureus* was presensitized with both Ab and C′ for sixty minutes at 37° C. Portions were then adjusted to 37° C. and to 0–2° C. and mixed with r.b.c. which had been equilibrated at the appropriate temperature. At the times charted in Fig. 1, samples were removed and the mixtures separated by low-speed centrifugation. The number of bacteria floating free in the fluid phase and the number adherent to the r.b.c. were recorded by dark-field examination. As

expected from previous assays, clearing of the fluid phase was rapid at 37° C., with a 50% end-point reached in about two minutes. In marked contrast, the rate was considerably retarded at 0° C. to 2° C., with about sixty minutes required for 50% reactivity. It should be emphasized that a high ratio of r.b.c. to bacteria was utilized to minimize any influence of temperature on the rate of contact of r.b.c. and bacteria.

This temperature gradient assumes an important significance in consideration of the nature of the linkage between the r.b.c. and the sensitized bacterium. The requirement for elevated temperature differs from the well-known maximal rate at low temperature of adsorption of virus to erythrocytes, and with the more-or-less constant rate of adsorption from 0° to 37° C. of: (1) bacteriophage to host bacterium (Tolmach and Puck, 1952); (2) protein antigens or inulin to tanned erythrocytes (Boyden, 1951); and (3) non-sensitized bacteria to erythrocytes at low pH (Nelson, unpublished). Although not definite, this observation suggests that I–A is not a simple adsorption phenomenon involving electrostatic bonds. The true nature of the linkage remains unknown.

In proceeding to a consideration of the second phase of I–A, it is necessary to pass over a rather large amount of information which has been obtained on the nature and reactivity of the r.b.c. surface. This second phase concerns the ability of leucocytes to phagocytize *in vitro* the B–Ab–C′ complex. Since various details on this aspect were published previously (Nelson, 1953), no experimental protocols will be shown. Suffice it to say that assays with a wide variety of organisms showed decisively that phagocytosis of the adherent bacteria was markedly enhanced as compared with controls in which B–Ab–C′ was floating free in plasma.

It seems important to review some findings of the past two months which indicate that I–A occurs *in vivo*. This project was accomplished at the London School of Hygiene and Tropical Medicine with the help of Dr. Joan R. Davis. Unfortunately these experiments were quite complicated from a technical standpoint, and it has not been possible to include in a single chart all the essential controls which were performed. The following two tables may be considered as typical of results obtained to date.

Table III: A sample of blood was removed from a normal, i.e. non-immune, monkey by

TABLE III.—THE LOCATION OF *D. pneumoniæ*, TYPE I, IN THE PLASMA OF BLOOD FROM A MONKEY AFTER INTRAVENOUS INJECTION OF ABOUT 25×10^5 MICRO-ORGANISMS

[Exper. 092755]

Blood collected into chilled ·002 *M* EDTA		No. of leucocytes per ml. of mixture $\times 10^3$	No. of bacteria per ml. undiluted blood taken from 0 to 6 min.
Whole blood		250	3,173
Plasma	Supernate from dextran	190	2,514
	Supernate from centrifugation	0	2,680
Erythrocytes	Deposit from dextran	60	96
	Deposit from centrifugation	140	306

cardiac puncture from 0 to 6 minutes after intravenous injection of about 25×10^5 *Diplococcus pneumoniæ*, type I. Separation of the erythrocytes from plasma by low-speed centrifugation in the cold and by dextran sedimentation, showed that over 90% of the bacteria were, as expected, in the plasma.

Table IV: The next table demonstrates the strikingly different type of results obtained in

TABLE IV.—THE RECOVERY OF PRE-SENSITIZED *D. pneumoniæ*, TYPE I, FROM BLOOD AFTER INTRAVENOUS INJECTION INTO A NORMAL MONKEY [EXPER. 093055] AND INTO A NORMAL RABBIT [EXPER. 100655]

	Blood samples collected by cardiac puncture				*In vitro* controls*			
	Monkey		Rabbit		Monkey		Rabbit	
Blood collected into chilled 0·002 *M* EDTA	No. per ml.	Per cent recovered	No. per ml.	Per cent recovered	No. per ml.	Per cent recovered	No. per ml.	Per cent recovered
Untreated	2,175	—	8,900	—	1,225	—	5,600	—
Plasma, Supernate from centrifugation	38	< 2	8,425	95	1,075	88	4,550	81
Erythrocytes, Deposit from centrifugation	2,200	100	243	3	0	0	30	< 1

*Presensitized bacteria mixed with blood samples in the presence of ·002 *M* EDTA which inhibits I–A, presumably by blocking fixation of C′ to the bacteria – Ab complex.

an immune monkey. For technical reasons, it was deemed advisable to sensitize the bacteria with Ab *in vitro* and then to inject the sensitized organisms intravenously into a normal host. Thus, the bacteria could be treated with a minimal amount of Ab, thereby diminishing the risk of agglutination which would seriously interfere with our measurements of the number of bacteria recovered. Essentially 100% of the presensitized bacteria were recovered with the erythrocytes from the monkey blood. To verify the significance of this result as it relates to I–A, mixtures of the presensitized bacteria with monkey blood were made *in vitro* in the presence of ethylene diamine tetra-acetate (EDTA) which inhibits I–A but presumably does not influence agglutination. About 88% of the bacteria remained in the plasma. Similarly the presensitized pneumococci remained in the plasma after injection intravenously into a rabbit, an animal whose erythrocytes do not react in I–A.

To return to the problem of the fate of the bacteria attached to the erythrocyte via I–A. The dynamic aspects of phagocytosis by leucocytes were reviewed in the film shown (kindly prepared by Dr. R. Robineaux at the Hôpital St. Antoine in Paris). Some general aspects of the film may be summarized as follows:

(1) A washed suspension of *Micro. aureus* was mixed with freshly collected human blood. Within fifteen minutes approximately 90% of the bacteria became adherent to the erythrocytes.

(2) Recordings were made of the phagocytosis of the adherent bacteria. The ease with which the phagocyte engulfed the adherent staphylococci was remarkable when compared with engulfment of single or agglutinated bacteria which were floating free in plasma.

(3) There was no phagocytosis of the erythrocyte.

(4) Numerous examples were noted of two or more erythrocytes attached to one bacterium or to a clump of bacteria.

(5) It was remarkable to observe the manner in which the leucocyte "scoured" the erythrocyte surface, producing marked deformity, and then moving to leave a normal-appearing red blood corpuscle. This would suggest that phagocytosis of adsorbed virus particles might occur under such circumstances, at least *in vitro*; the possibility is being studied in a current research project.

In concluding these remarks on I–A *in vitro* and *in vivo* it seems essential to make one comment on the erythrocyte which perhaps now may be envisaged as possessing an importance which goes beyond the simple transport of O_2 to the tissue.

The lack of reactivity of erythrocytes from species other than monkey, baboon and man is perplexing, particularly if one wishes to ascribe to I–A a general role in host defence. However, the species specificity is no more remarkable than that which exists in other fundamental immunological phenomena. For example, one has only to consider the variety of animal species in which certain fractions of C′ are lacking or in a low titre. Despite this, and up until the advent of "properdin," there were not many immunologists who seriously disputed the role of C′ in bactericidal and bacteriolytic phenomena. This, of course, is only evading the issue by citing other equally difficult and, at the moment, unexplainable problems. On the other hand, it might be argued that the reactivity of erythrocytes in I–A constitutes an evolutionary development in the so-called higher species.

REFERENCES

BOYDEN, S. V. (1951) *J. exp. Med.*, **93,** 107.
BROOM, J. C., BROWN, H. C., and HOARE, C. A. (1936) *Trans. R. Soc. trop. Med. Hyg.*, **30,** 87.
DUKE, H. L., and WALLACE, J. M. (1930) *Parasitology*, **22,** 414.
LEUPOLD, F. (1928) *Z. Hyg. Infektkr.*, **109,** 144.
MAYER, M. M., LEVINE, L., RAPP, H., and MARUCCI, A. (1954) *J. Immunol.*, **73,** 443.
NELSON, R. A. (1953) *Science*, **118,** 733.
——, and LEBRUN, J. (1956) *J. Hyg.*, In press.
TOLMACH, L. J., and PUCK, T. T. (1952) *J. Amer. chem. Soc.*, **74,** 5551.

Miss Muriel Robertson: Red cell adhesion has been known for many years in pathogenic trypanosomes. The first paper was Rieckenberg's in 1917 and while the Rieckenberg phenomenon and the red cell adhesion test may not be exactly the same they are very similar. The best accounts, which include good reviews of the subject, are to be found in the paper of Davis and Brown (1927) and that of Brown and Broom (1938). The red cell adhesion test, as defined by the last-named authors, is a specific serological reaction and consists of incubating together trypanosomes, immune serum, complement and human red cells. If the serum is homologous, the red cells become firmly adherent to the trypanosomes. Duke and Wallace also worked with this test in Africa with pathogenic trypanosomes in 1930.

REFERENCES

BROWN, H. C., and BROOM, J. C. (1938) *Trans. R. Soc. trop. Med. Hyg.*, **32,** 209.
DAVIS, L. J., and BROWN, H. C. (1927) *Trans. R. Soc. trop. Med. Hyg.*, **21,** 113.
DUKE, H. L., and WALLACE, J. M. (1930) *Parasitology*, **22,** 414.

Growth of Normal and Neoplastic Mammalian Cells on the Chick Chorion

By J. P. M. Bensted, M.B., B.Chir.
Department of Pathology, Guy's Hospital, London

Introduction

The use of the chick embryo in biological research is by no means a recent innovation for it was in 1911 that Peyton Rous and Murphy first transplanted a chicken sarcoma to the chick embryo by inoculation and obtained successful growth. At the same time they also suggested a virus origin of tumours by successfully inducing tumour growth in the embryo with cell-free extracts of chicken sarcoma. In the following year, Murphy (1912) transplanted an heterologous tumour, the Jensen rat sarcoma, to the embryo and maintained it for forty-six days outside its host by serial passage from egg to egg.

Since that time, the value of the chick embryo has become apparent in many other fields, particularly to embryologists in the study of embryonic differentiation. Amongst the workers in this field were Dantchakoff (1916), Hoadley (1924) and Willier (1924) who made a particular study of the developmental potencies of the early chick blastoderm and showed that transplantation could be effected between embryos of widely unrelated individuals such as birds and mammals.

Later, virus workers realized the enormous possibilities of the developing chick embryo in the cultivation of viruses following the demonstration by Woodruff and Goodpasture (1931) of the growth of fowlpox on the chorio-allantoic membrane. Shortly afterwards Burnet (1936) produced his M.R.C. monograph on the use of the developing egg in virus research.

More recently the technique has been employed in the field of cancer research by Karnofsky and his associates (1952) of the Sloan-Kettering Institute.

Principles

The general principles underlying the use of the chick embryo are twofold. In the first place, the embryo is unable to produce antibodies and is thus immunologically unresponsive to foreign tissues. Secondly, the chorio-allantoic method of inoculation provides a highly vascular membrane from the eighth day of incubation onwards. In the embryo, the chorio-allantoic membrane functions as a respiratory organ and only regresses just before hatching. It is a very thin, delicate, translucent structure lying immediately beneath the shell membrane with an ectodermal layer separated by vascular mesenchyme from the entodermal layer.

Method

The technique employed in these studies was along the lines indicated by Beveridge and Burnet (1946), in which a fairly large area of chorio-allantoic membrane is exposed by the creation of an artificial air-space. When tumour is used, it is removed from a freshly sacrificed host and minced up into fragments about 1–2 mm. diameter in Krebs-Ringer phosphate containing 1,000 units each of penicillin and streptomycin/ml. The fragments (1–4 in number) are then placed directly on the membrane of the 8–9 day embryo. When skin fragments are used they average about 3×1 mm. and are placed corium side down. The window in the shell is sealed with paraffin wax and a cover glass and the egg returned to the incubator for the required time.

As an alternative to the chorio-allantoic route which has been chiefly used in this work, the yolk-sac and intravenous routes of inoculation, the latter from the thirteenth day of incubation onwards, have also been employed with varying success.

Advantages and Limitations

In addition to the great advantages of immunological indifference already mentioned, the embryo provides a sterile, highly nutritious medium for the graft, with the provision of growth factors and some hormones; moreover, its use requires no elaborate equipment. On the other hand, the method has disadvantages in that direct microscopic examination of the growing tissue is not possible and that growth is limited by the hatching of the chick though serial transplantation is possible and, indeed, Karnofsky *et al.* (1949) reported cultivation of a mouse sarcoma for a year. In summary, then, the technique might be regarded as a compromise between *in vitro* and *in vivo* tissue culture.

Observations

Normal Tissues

(*a*) *Skin.*—Thin fragments of skin from the guinea-pig ear, measuring about 3×1 mm. and including dermis and its vessels, were used. The explants were rapidly and readily

vascularized and were allowed to remain on the membrane for eight to nine days. Histological examination showed active mitosis in the basal layer and cornification, and the capillaries were full of nucleated chick red cells (Fig. 1).

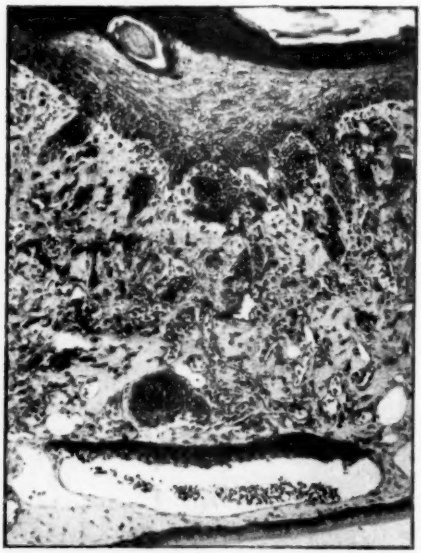


FIG. 1.—Skin from the ear of a guinea-pig, growing on the chorio-allantoic membrane for ten days. The graft, seen in the upper half of the field is well vascularized. A large chick vessel adjacent to the allantois is seen in the lower half. (H. and E. × 147.)

(*b*) *Vaginal epithelium.*—In collaboration with Professor Robson of the Department of Pharmacology, Guy's Hospital, an attempt was made to study the effect of local application of œstrogens on the cornification of immature mouse vaginal epithelium. In these experiments whole vaginas of 21–24-day-old immature female mice were removed, opened longitudinally and cultivated on the membrane for six to seven days. Solid œstrogen implants were placed on the membrane close to the graft, but it was not possible to find a dose of œstrogen, administered in this way, which did not kill the graft. However, greater success was obtained with yolk-sac administration of œstrogen. It would seem, from the work of Willier (1952) that the host's sex hormones do not influence the graft as might have been anticipated.

Neoplastic tissues.—Observations were made on mouse tumours obtained through the kindness of Dr. P. A. Gorer, including a benzpyrene (BP_8)-induced sarcoma cultivated in both ascitic and solid phase, a solid mammary tumour ($C3H/MT_2$), an ascites mammary tumour (MTC/1A) and a lymphogenous leukosis (E.L.4).

Tumour of the solid form was minced and transplanted in fragments 1–2 mm. diameter and the ascites tumour inoculated as a thick suspension on the membrane (or into the yolk-sac in some experiments).

The sarcomata grew well with a 70% "take" rate. They grew rapidly and became well vascularized and quite large; one graft weighed 1·3 grams after fourteen days' growth, representing some fifty-fold increase in mass (Figs 2 and 3). Histological examination showed numerous, actively dividing cells, the tumour continuing to grow on re-transplantation back into a host of the same strain.

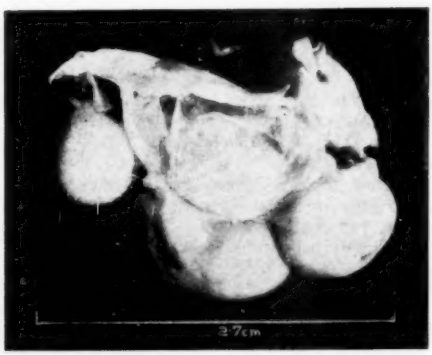


FIG. 2.—Nodules of growth resulting from the inoculation of 0·1 ml. undiluted mammary ascites tumour directly on to the chorio-allantoic membrane. Seen after eleven days' growth.

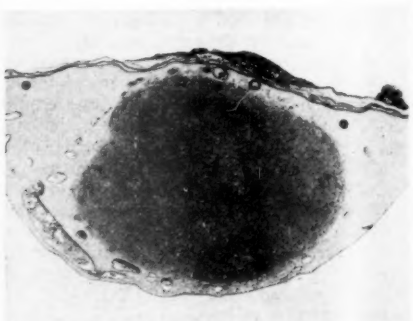


FIG. 3.—Appearance of BP_8 ascites tumour after eleven days' growth. Original, but now necrotic, inoculum on ectodermal (upper) surface with ascites cells growing in the mesenchymal layer. (H. and E. × 13.)

Several host embryos were examined to determine the presence of visceral metastases, and none was found. Also several host embryos were allowed to hatch and, apart from some growth retardation in the first few weeks of life, showed no abnormal features.

The mammary tumour grew equally well (Fig. 4) and preserved its morphology, a feature which cannot so readily be demonstrated by *in vitro* tissue culture methods. Stromal reaction was minimal.

The leukosis (E.L.4) grew with much greater difficulty and only a 20% average "take" rate was achieved, despite attempts to increase this by the use of hyaluronidase. No serious attempt was made to cultivate human tumours.

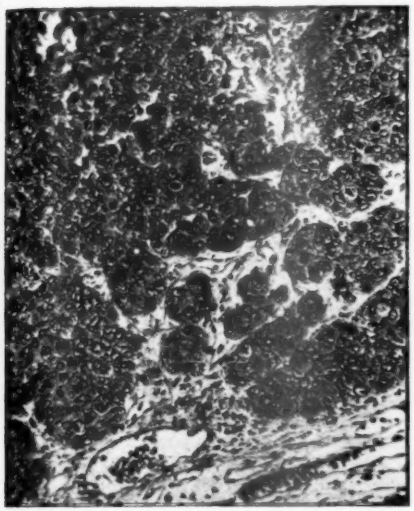


FIG. 4.—A mammary carcinoma ($C3H/MT_2$) showing its characteristic morphology after ten days' growth on the membrane. It is well vascularized and shows little stromal response. (H. and E. × 175).

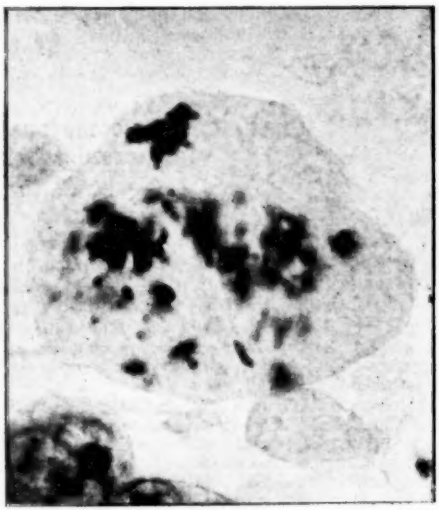


FIG. 5.—Appearance of a BP_8 sarcoma cell under the influence of nitrogen mustard (0·1 mg. HN_2 into the yolk-sac for forty-eight hours: embryo apparently unaffected), showing an abnormal mitotic figure, possibly a metaphase. (Feulgen preparation × 1,675.)

APPLICATION OF THE TECHNIQUE

The method has several possible applications, one of which is its use in the evaluation of chemotherapeutic agents in the treatment of neoplasia. The observations of Dagg *et al.* (1954) on the effect of nitrogen mustard have been confirmed, and the peculiar effect of the drug on the chromosomes, causing bizarre mitoses and chromosome breakage, was frequently seen (Fig. 5).

Mirand and Hoffman (1955) were able to modify the normal tumour-host relationship of mouse tumours by cultivating the tumour in the egg for one or more passages, and showed that, on return to the original strain, increased susceptibility to tumour grafts occurred in strains normally insusceptible to the tumour.

Billingham, Brent and Medawar (1953) demonstrated that active acquired tolerance to foreign tissues in the adult could be created by exposure of the embryo to foreign living cells. Hence it might be possible to cause heterologous tumours to grow in the adult chick by making use of this property. However, some preliminary experiments along these lines have not proved fruitful, for two possible reasons. First, it is not certain, at least with chorio-allantoic grafts, that the tumour cells are entering and multiplying in the fœtal circulation and thus producing a true chimæra. Secondly, the biological gap between bird and mammal may be too wide.

I should like to acknowledge the interest which Professor G. Payling Wright has shown in this work and the encouragement he has given me.

REFERENCES

BEVERIDGE, W. I. B., and BURNET, F. M. (1946) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 256.
BILLINGHAM, R. E., BRENT, L., and MEDAWAR, P. B. (1953) *Nature, Lond.*, **172,** 603.
BURNET, F. M. (1936) *Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 220.
DAGG, C. P., KARNOFSKY, D. A., TOOLAN, H. W., and RODDY, J. (1954) *Proc. Soc. exp. Biol., N.Y.*, **87,** 223.
DANTCHAKOFF, V. (1916) *Amer. J. Anat.*, **20,** 255.
HOADLEY, L. (1924) *Biol. Bull., Wood's Hole*, **46,** 281.
KARNOFSKY, D. A., PARISETTE, L. M., PATTERSON, P. A., and JACQUEZ, J. A. (1949) *Acta Un. int. Cancr.*, **6,** 641.
——, RIDGWAY, L. P., and PATTERSON, P. A. (1952) *Ann. N.Y. Acad. Sci.*, **55,** 313.
MIRAND, E. A., and HOFFMANN, J. G. (1955) *Proc. Soc. exp. Biol., N.Y.*, **88,** 656.
MURPHY, J. B. (1912) *J. Amer. med. Ass.*, **59,** 874.
ROUS, P., and MURPHY, J. B. (1911) *J. Amer. med. Ass.*, **56,** 741.
WILLIER, B. H. (1924) *Amer. J. Anat.*, **33,** 67.
—— (1952) *Ann. N.Y. Acad. Sci.*, **55,** 159.
WOODRUFF, A. M., and GOODPASTURE, E. W. (1931) *Amer. J. Path.*, **7,** 209.

Contiguous Sarcomatous and Gliomatous Tissue in Intracranial Tumours [*Abstract*][1]

By L. J. RUBINSTEIN, M.D.

The Bernhard Baron Institute of Pathology, The London Hospital

THE purpose of this communication is to describe briefly, and largely from the histological point of view, 4 cases of primary intracranial tumour in which sarcomatous and gliomatous tissue lay in juxtaposition. It is believed that in these cases the neoplastic activity of one type of tissue was closely related to the presence of malignancy in the other.

Case 1.—A woman of 53 died after a three weeks' history of headache and nausea. Necropsy revealed a right fronto-temporal meningioma of fibroblastic type which invaded the brain anteriorly and ventrally. At its periphery, the tumour exhibited an intimate mixture of fibrosarcomatous and gliomatous elements.

Case 2.—A woman of 21 had been suffering from left-sided epileptic fits and from right temporal headaches for five years. One month before admission, the headaches grew more frequent and more severe. A circumscribed right temporal tumour, presenting superficially and attached to the leptomeninges, was enucleated. Microscopically, it proved to be a spindle cell sarcoma, probably arising from the pia. At its periphery, there was an uneven rim of tissue composed of pleomorphic and anaplastic glial cells, indistinguishable in appearance from a glioblastoma multiforme. This tissue was itself clearly demarcated from a fringe of cortex exhibiting ordinary fibrillary gliosis. The patient was known to be alive and well more than three years after the operation.

Case 3.—A man of 64 had been suffering from epileptic fits for three months and from headaches and drowsiness for four weeks. A right temporal tumour attached to the dura was partly removed. Two months later his symptoms returned and he went gradually downhill, dying within a year of the onset of illness. Necropsy revealed a large hæmorrhagic recurrence. Microscopically, the tumour at biopsy consisted of two types of tissue which were closely interrelated: (*a*) fibrochondrosarcoma, which lay on the whole in the more central portions of the tumour; (*b*) glioblastoma. The tumour is believed to be primarily a fibrochondrosarcoma, presumably of meningeal origin, the gliomatous elements having arisen from a neoplastic change in the adjacent neuroglia.

The view is held that in Cases 1, 2 and 3 a secondary neoplastic change took place in the glia in response to the presence of an invading mesodermal tumour.

Case 4.—A man of 48 had been suffering from right temporal headaches for a year and, more recently, from ataxia and attacks of vomiting. A well-defined and apparently non-infiltrating right temporal tumour, situated 15 mm. below the surface, was excised. Outwardly, it resembled a meningioma, but its relation to the meninges was uncertain. Microscopically, it consisted of closely intermingled fibrosarcomatous and glioblastomatous tissue. There was also, around and within its blood vessels, a remarkable proliferation of cells which exhibited malignant features.

After a good immediate recovery, the patient relapsed six weeks later and died shortly after from a large recurrence.

It is suggested that in this case the tumour was originally a glioblastoma multiforme in which one or more foci of vascular proliferation were the site of origin of a secondary sarcomatous change. It appears similar to two of the tumours recently described by Feigin and Gross (1955, *Amer. J. Path.* **31,** 633).

Professor Dorothy S. Russell: Dr. Rubinstein's series of cases is instructive in that they apparently demonstrate the induction of neoplasia in one tissue by a neighbouring malignant growth of different tissue-origin. Though this has been said to occur in the stroma of carcinomas in other parts of the body, the central nervous system and its meninges are particularly rewarding in this type of study, owing to the clarity with which the interacting tumour elements can be distinguished histologically.

[1]To be published in full in the *Journal of Pathology and Bacteriology*.